Effect of robotic gait training on the post-stroke gait pattern

Evaluation of LOPES II

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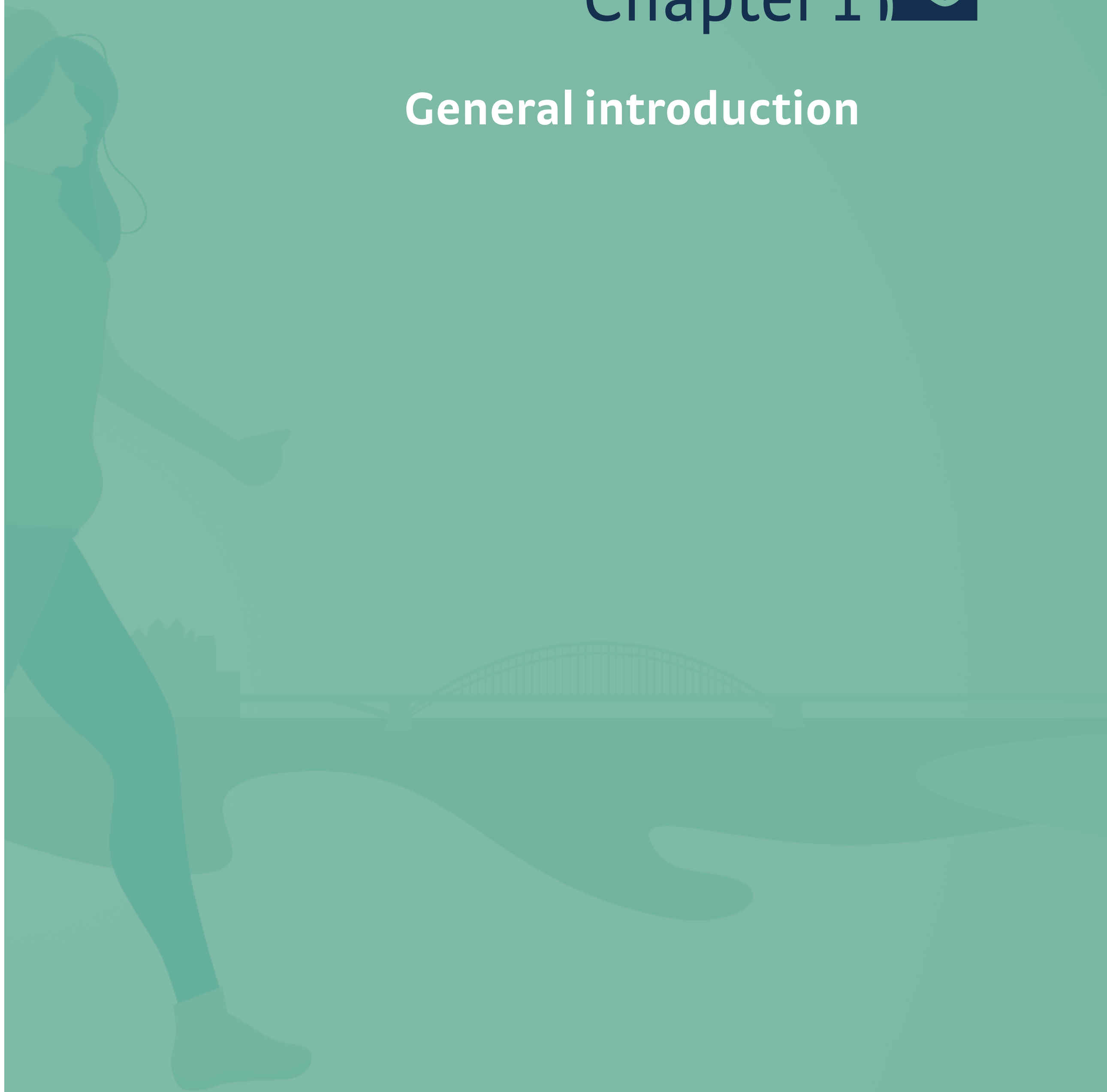
Chapter 1

General introduction



General introduction

Cerebrovascular accident, also referred to as stroke, is a major cause of disability in elderly worldwide[1]. A stroke is defined as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin”[2]. A stroke occurs when the blood flow to the brain is reduced or disrupted, causing deprivation of oxygen and glucose to the perfused brain tissue[3]. The majority of strokes is caused by occlusion of a blood vessel by a blood clot or embolus (ischemic stroke)[4], whereas the minority (approximately 20%)[3] is caused by rupture of a blood vessel due to increased blood pressure, trauma or aneurysm (hemorrhagic stroke)[4]. If the blood flow is not restored in time, the brain tissue will get damaged and eventually die.

The consequences of stroke vary between individuals, with the severity of stroke depending on the size and location of the brain lesion[5]. They may include a variety of cognitive, sensory, and motor impairments. A stroke in the (primary) motor cortex is associated with contralateral hemiparesis of the upper and/or lower limbs. In general, more severe motor impairments are observed in the distal compared to the proximal body parts in people after stroke[6]. And the more severe the motor weakness, the higher the chance of increased involuntary muscle tone upon muscle stretch or at rest, so called ‘spasticity’. If stroke leads to substantial damage of the corticospinal tracts, which are typically used to control fine motor skills, stroke survivors may have to rely on the reticulospinal tracts to control both proximal and distal movements[7]. However, use of such brainstem descending pathways results in loss of fine motor control, with a dominant flexion pattern in the upper extremity and a dominant extension pattern in the lower extremity. The motor impairments after unilateral supratentorial stroke may thus include loss of motor control, muscle weakness and spasticity.

Motor recovery after stroke

After stroke, motor capacity may improve over time, with most functional recovery observed in the first months after stroke onset[8,9]. Functional recovery will become smaller over time, until it reaches a plateau at about six months post stroke[10-12]. Post-stroke functional recovery is suggested to be influenced by three mechanisms. First, behavioral restitution of function refers to “a return towards more normal patterns of motor control with the impaired effector, reflecting the process towards true neurological recovery”[13]. This takes place in the subacute phase after stroke (until 3-6 months post onset)[13], but mainly during the first 6-8 weeks. There is little evidence that behavioral restitution of function can be facilitated by physical training[12,14]. Although physical training may stimulate experience-dependent neural plasticity, behavioral restitution of function is generally assumed to be the result of spontaneous neurological recovery. Second, behavioral substitution of function refers to “the learning and use of compensatory strategies that involve alternative effectors, joints, muscles or kinematics to accomplish a task”[14]. Behavioral substitution of function takes place already in the subacute phase post stroke, thereby complementing behavioral restitution of function, but may continue into the chronic phase post stroke (> 6 months post onset)[13]. In contrast to behavioral restitution of function, there is ample evidence that behavioral substitution of function can be promoted by task-specific training[12]. A third mechanism of functional recovery is the remission of “learned non-use“, which may result in additional functional recovery through the utilization of latent, residual motor capacity[15,16]. Such residual capacity may have become latent due to the initial inability to move the limbs in the (sub-)acute phase and/

or slow subsequent functional recovery leading to a great effort required to use the paretic limb in later stages. This increased effort causes fatigue and negative reinforcement, which eventually results in a learned suppression of the residual motor capacity of the paretic limb. Although there is a growing evidence for the effect of task-specific training on the remission of learned non-use of the upper extremity in chronic stroke survivors[17-19], similar evidence for the lower extremity is limited[20,21].

Although all three mechanisms may contribute to some degree of functional recovery after stroke, post-stroke motor performance remains limited in many hemiparetic patients despite current rehabilitation programs[22,23]. The studies described in the present thesis will specifically focus on new avenues for gait rehabilitation in the subacute and chronic phases after unilateral supratentorial stroke, causing lower extremity motor impairments.

Gait

As a result of lower extremity motor impairments, gait capacity is often reduced after stroke[24]. The hemiparetic gait pattern is associated with a reduced ability to perform activities of daily life[25], limited community ambulation[26], and reduced quality of life[26]. Consequently, improving gait capacity is a major rehabilitation goal for many individuals in the subacute phase post stroke[27], as well as during the subsequent chronic phase[28,29]. Early gait rehabilitation after stroke is generally focused on regaining gait independence and optimizing the gait pattern, whereas the focus of gait rehabilitation gradually shifts towards improving gait adaptability to be able to deal with the challenges of complex daily life situations. These three domains of gait (gait independence, gait pattern, and gait adaptability) and their relationship with balance control and paretic leg motor control are shown in Figure 1, and will be further discussed in the following section.

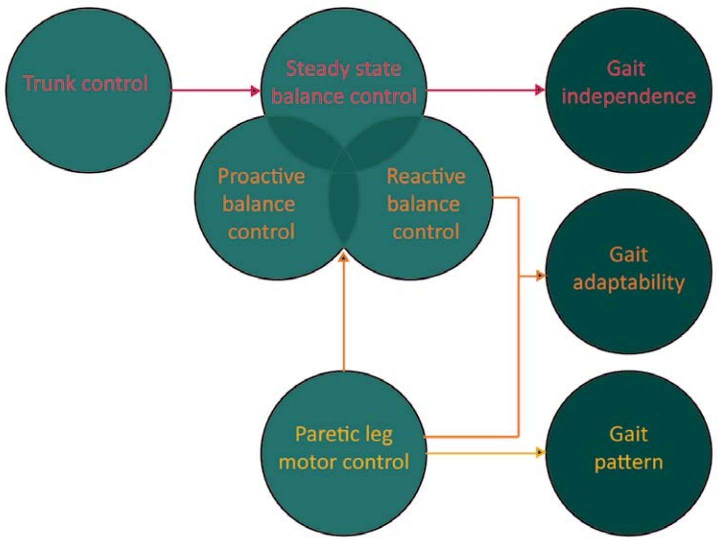


Figure 1. Theoretical framework on dynamic balance and gait after stroke (reprinted with permission from H.J.R. van Duijnhoven[30].

Gait independence refers to an individual's ability to walk with or without a walking aid, but without the physical assistance from another person. Gait independence can be assessed using the Functional Ambulation Categories (FAC), a valid and reliable tool for classifying the level of support or supervision needed for safe ambulation after stroke[31,32], with scores ranging from nonfunctional ambulation (0) to independent ambulation on (un)even surfaces, inclines or stairs (5). Within the first week post onset, only 30-37% of the acute stroke survivors admitted to inpatient rehabilitation are independent ambulators[33,34], whereas the majority of stroke survivors admitted to rehabilitation cannot walk without the assistance from one or more persons to support their balance and gait. Following rehabilitation, approximately 64-85% of the individuals after stroke regain independent walking capacity[23,33,34]. A major determinant for regaining gait independence is steady state balance control[35]. Early control of trunk movements and sitting balance are considered key predictors of standing balance and independent gait at 6 months post stroke[36,37].

The gait pattern is characterized by a sequence of lower limb movements, combined with upper extremity arm swing, and upright trunk posture. Conventional methods used to evaluate the gait pattern are clinical examination or visual gait observation[38]. Such observational assessment may provide information about spatiotemporal gait asymmetry[39-41] and reduced gait speed[22,42] as commonly observed after stroke. However, a disadvantage of observational methods is the lack of objective and accurate assessment of gait kinetics and kinematics. A more objective and accurate way to assess the entire gait pattern is three-dimensional (3D) gait analysis, in which infrared cameras and force plates measure the position of reflective markers attached to the body segments and the ground reaction forces during gait, respectively. Such 3D-gait analysis provides insight in the gait kinetics (e.g. joint forces, moments, and power), kinematics (e.g. joint angles and velocities), as well as spatiotemporal parameters (e.g. step length and swing duration). In healthy adults, the gait pattern generally meets the five prerequisites of normal gait (i.e. stability during the stance phase, foot clearance during the swing phase, foot prepositioning and adequate step length at the end of swing, and energy conservation)[38], and is typically 'symmetrical'[43]. In contrast, due to a combination of gait impairments and compensatory strategies, the post-stroke gait pattern is often asymmetrical. After stroke, impaired leg motor control may cause, for example, knee instability during early and midstance[40,44], reduced knee flexion during swing[40,45], or pes equinovarus during swing and loading[46]. In addition, impaired ankle push-off at the paretic side is often observed during terminal stance[40,46], resulting in reduced anteriorly oriented ground reaction forces (i.e. propulsion). Such reduced propulsion by the paretic leg during terminal stance has a major impact on the post-stroke gait pattern, as it is associated with reduced gait speed[47], impaired swing initiation[40,45], and reduced gait capacity[48,49]. To overcome their gait impairments, people with stroke often use compensatory movements, such as abduction of the paretic leg and pelvic hike (so-called 'circumduction') to facilitate foot clearance[50,51] or exaggerated paretic hip 'pull-off' to compensate for loss of 'push-off' power in order to swing the paretic leg forward[52,53]. Unfortunately, the use of compensatory movements is associated with increased energy consumption and reduced gait efficiency[40,48,54,55], which has a negative impact on functional gait capacity.

Gait adaptability is necessary to safely adapt the gait pattern to changing environmental demands or individual behavioral goals. For example, people may change gait speed while crossing the street to avoid cars; they may adapt their step length to cross obstacles; or adjust their step width to keep balance when walking on unstable surfaces. Gait adaptability can be assessed using clinical tests like the Functional Gait Assessment[56] or the modified Emory Functional Ambulation Profile[57]. Gait adaptability can also be assessed with instrumented treadmills like the C-Mill[58] or overground solutions like the Interactive Walkway[59] using projected obstacles or stepping targets. Post-stroke gait adaptability is often reduced[60-62], probably because the coordinative adaptations required for complex gait tasks are a huge challenge for many stroke survivors[60]. Indeed, in order to show sufficient gait adaptability, individuals need to have a sufficient level of paretic leg motor control – in addition to sufficient balance control – to be able to proactively and reactively respond to changing environmental demands (see Figure 1).

This thesis describes four studies targeting different aspects of the gait pattern in the subacute and chronic phases post stroke. The evaluation of the gait pattern focuses on the kinematic and kinetic gait characteristics, more than on the spatiotemporal gait characteristics. Kinematic and kinetic aspects of the gait pattern are evaluated before and after multiple sessions of conventional gait training or before and after single or multiple sessions of robotic gait training.

Conventional gait training

A key element in post-stroke gait rehabilitation is physical therapy in the form of conventional training aimed at restoring gait capacity. Typically, conventional gait training includes overground or treadmill walking[63], sometimes augmented with muscle strength exercises[64,65], use of body-weight support systems[66], functional electrical stimulation[67,68], or biofeedback[69,70]. Conventional gait training is commonly supervised by a physical therapist who can manually assist lower extremity movements or control balance to facilitate an effective stepping pattern. In general, such training starts within the first days post stroke, and may continue into the chronic phase[12]. According to the latest insights, conventional gait training should include intensive and task-specific training with a high number of repetitions in all phases post stroke[71] in order to stimulate experience-dependent neural plasticity mechanisms[72] and promote motor learning and recovery[29,73,74].

Current evidence indicates that conventional gait training is effective for improving gait independence, gait speed and endurance in the subacute phase after stroke[75,76], but these findings should be interpreted in the light of the spontaneous neurological recovery that may be present. Also in the chronic phase post stroke, gait speed and endurance improved following conventional gait training[77]. Unlike the evidence for the effect of conventional gait training on gait capacity, the effect of conventional gait training on the post-stroke gait pattern is very limited. Conventional gait training did not change the timing of muscle activation in the paretic leg of subacute stroke survivors[78,79]. In addition, most clinical studies did not find an effect of overground gait training on gait kinematics or kinetics in subacute[80-82] or chronic stroke survivors[83]. A possible explanation for the lack of training effects may be the difficulty for physical therapists to provide adequate manual support of balance and trunk movements and concurrently attend to the specific training goals of the paretic leg, thereby allowing stroke survivors to focus their attention on the specific training goal. Besides, providing manual assistance during conventional gait training may place a high physical burden on therapists[84], which may potentially limit training duration and intensity[85]. To overcome these drawbacks, mechanically assisted gait training was introduced in rehabilitation of neurological patients.

Robotic gait training

Treadmill-based robotic gait trainers can provide intensive, task-specific, and repetitive exercise early post stroke by mechanically assisting or constraining lower extremity movements. Robotic gait trainers make use of an exoskeleton attached to the pelvis and/or lower extremities that actively controls the movements of one or more joints while the participant walks on the treadmill. The movements that can be performed in robotic gait trainers depend on the number of degrees of freedom. Robotic gait trainers with ample degrees of freedom allow participants to walk with a fairly natural gait pattern[86,87]. They also allow the performance of compensatory movements if necessary. The powered degrees of freedom define what movements can be assisted during the training. Most robotic gait trainers have limited their powered degrees of freedom to the sagittal plane (e.g. first generation Lokomat[88], AutoAmbulator[89], ALEX[90]). In order to allow active balance control, (powered) degrees of freedom in the frontal plane are frequently implemented in newly designed robotic gait trainers (e.g. LOPES II[91], ALEX III[92]).

Most robotic gait trainers use a position-controlled or impedance-controlled algorithm to provide mechanical assistance. Position-controlled robots move individuals along a pre-defined reference trajectory. An example of a position-controlled robotic device is the first generation Lokomat[88]. Drawbacks of position-controlled robots are that movement variability is reduced to a minimum[86,93]. In addition, muscle activity may decrease during training as participants can rely on the robot to move their legs[94,95]. As movement variability and active participation are considered advantageous for motor learning[96,97], use of position-controlled algorithms in gait rehabilitation of stroke survivors is associated with limited effectiveness[98]. Hence, to enhance movement variability and active participation during the training, impedance-controlled robots have been developed. Impedance-controlled robots control the forces exerted on the individual, instead of the position of body segments. When the individual deviates from the pre-defined reference pattern, the applied guidance force will increase as a function of robotic stiffness[99]. A low impedance mode allows participants to walk with minimal hindrance from the robot and optimizes movement variability, whereas robots with high impedance act more or less like position-controlled devices. Examples of impedance-controlled robots are LOPES[91,100], ALEX[90,92], and the later versions of Lokomat[101,102]. Some of these impedance-controlled robots use an assist-as-needed (AAN) approach[103], which generally refers to robots that apply minimal levels of assistance needed for performing specific gait tasks[103-106]. However, in the literature the definition of AAN has not yet been clearly defined. Studies may refer to the use of an AAN approach when the robotic gait trainer allows support of the impaired gait tasks[107-109], allows free movement of unimpaired gait tasks[109,110], or permits modification of the assistance level[91,107,111] and/or (real-time) adjustments of the assistance level to the individual's needs[103,110,112]. In general, use of an AAN approach is advocated to encourage people to be actively involved in the training. In this way, use of robotic gait trainers with an AAN approach might improve the efficacy of gait rehabilitation after stroke[113].

Although robotic gait training is commonly used in the gait rehabilitation of neurological patients, its advantage compared to conventional gait training in stroke survivors is still subject of debate. Recent reviews and meta-analyses have shown that, compared to conventional gait training alone, non-ambulatory individuals in the subacute phase post stroke are more likely to reach independent gait capacity and increase their gait speed following robotic gait training[114], preferably combined with conventional gait training[115-117]. On the other hand, some studies reported better walking capacity after therapist-assisted gait training compared to similar dosage of robotic gait training in stroke survivors[86,118]. Evidence for the effect of robotic gait training on the post-stroke gait pattern is even less extensive. Robotic gait training has been suggested to enhance paretic motor control[119,120], temporal gait parameters[119-122], gait kinematics[121,123-125] and kinetics[121,123,126], but these results should be interpreted with caution, as most studies did not include a control group[119,123,124,126] or implement follow-up measurements[119-123]. Hence, further investigation of the effect of robotic gait training on the post-stroke gait pattern is warranted.

This thesis focuses on the effect of treadmill-based robotic gait training on the post-stroke gait pattern. Robotic gait training was provided by a non-commercially available AAN robotic gait trainer, the LOPES II[91] (for a detailed description of LOPES II see Box 1). The LOPES II has multiple degrees of freedom in both the frontal and sagittal planes, and allows selective support of specific impaired subtasks of gait, and adjustment of the general impedance levels. Use of such a highly sophisticated robotic gait trainer may provide the ideal training circumstances for improving the post-stroke gait pattern.

Box 1. LOPES II

The robotic gait trainer LOPES II has been developed by the University of Twente, in collaboration with commercial parties MOOG and Demcon, and clinical partners Roessingh Research and Development and the Sint Maartenskliniek. LOPES II consists of an exoskeleton, a treadmill and a body weight support system (see Figure 2). The exoskeleton is attached to the participant's pelvis and lower limbs, using a pelvic harness, clamps around the upper part of the tibia, and foot brackets. The robot has multiple degrees of freedom, actuating the mediolateral and anterior-posterior pelvis translations, hip abduction/adduction and flexion/extension, and knee flexion/extension. In addition, ankle motion (plantarflexion/dorsal flexion, inversion/eversion, endorotation/exorotation) and pelvic rotations are free. Passive toe lifters can be added to support the ankle dorsiflexion movement during swing. Furthermore, pelvic motion can be mechanically constrained, reducing the mediolateral and rotational movements to a minimum. As the mechanical legs are located behind the participant, little alignment is needed (leading to a short donning time) and arm swing is allowed.

The LOPES II uses an assist-as-needed (AAN) approach to move participants along a predefined reference pattern. The applied guidance force depends on the measured deviation from this reference trajectory and the stiffness of the robot. It can be set from minimal impedance (minimizing interaction forces between the robot and the participant) to full assistance (more or less similar to position control). The guidance force is set in two parts: the general and the specific guidance force. The general guidance force is applied to the entire gait cycle and thus remains constant, whereas the specific guidance force is applied to specific subtasks of gait and may vary between specific intervals of the gait cycle (e.g. support of knee flexion during swing to facilitate foot clearance). The subtasks of gait that can be supported include: 1) stability in the stance phase, 2) foot clearance during the swing phase, 3) prepositioning of the foot at the end of swing, 4) weight shifting, and 5) adequate step length. During training, force and position sensors continuously measure the interaction forces between the robot and the participant and the segmental positions and joint angles, while a force plate installed underneath the treadmill determine the vertical ground reaction forces and the position of the center of pressure. Together, the collected data is used to control the interaction forces between the robot and the participant, and to provide online feedback about the participant's performance during the training.

Training with the LOPES II is supervised by an experienced LOPES trainer. At the first training, anthropometric data is collected to adjust the pre-defined reference pattern derived from healthy control subjects to the individual's height and selected gait speed. During the training, the level of guidance force, body-weight support, gait speed (0.1-3.0 km/h) and gait parameters (e.g. weight shifting amplitude, step length etc.) are adjusted by the physical therapist through a graphical user interface. Animations and graphical representations of the participant's performance relative to the reference pattern are provided by the LOPES II, and the participant receives verbal feedback from the therapist.

In 2014 the LOPES II was installed in two rehabilitation centers in the Netherlands: Roessingh center for rehabilitation (Enschede) and the Sint Maartenskliniek (Nijmegen).

Figure 2. Robotic gait trainer LOPES II

Outline thesis

This thesis focuses on the improvement of different aspects of the gait pattern using robot technology in various phases after stroke. Two main aims will be addressed. First, I aim to assess the potential after-effects of additional degrees of freedom in robotic gait trainers on the overground gait pattern of healthy adults (Part 1). Second, I aim to determine whether training in a robotic gait trainer with multiple degrees of freedom can improve different aspects of the overground gait pattern of individuals in the subacute or chronic phase after stroke. These gait aspects include center-of-mass movements, joint kinematics and propulsion measures (Part 2).

Part 1 of this thesis contains Chapter 2, in which we pose the research question whether there are immediate after-effects of a single session of robotic gait training with mechanically constrained or supported degrees of freedom around the pelvis on the overground gait pattern in healthy adults in order to better understand any possible (undesirable) effects of such training.

In Part 2 of this thesis we will evaluate the effect of robotic gait training on the hemiparetic gait pattern. As relearning and optimizing gait is an important rehabilitation goal early after stroke, Chapter 3 describes a randomized controlled trial to compare the effect of robotic gait training – using an assist-as-needed approach and multiple degrees of freedom (in LOPES II) – with conventional gait training on individually impaired aspects of the gait pattern in subacute stroke survivors (*LOPES-Arts study*; see Box 2, case 1). It is expected that robotic gait training might be superior to conventional training for improving mechanical work, gait kinematics related to pre-defined training goals, spatiotemporal gait parameters, and functional gait tasks. In Chapter 4 an overview is provided of the current evidence for the effectiveness of training interventions to improve propulsion of the paretic leg in stroke survivors. In addition, general characteristics of interventions that may improve post-stroke propulsion are identified. In Chapter 5 we investigate the effect of robotic gait training with the LOPES II on propulsion symmetry, gait speed, functional gait tasks and mobility in chronic stroke survivors (*I-PICS study*; see Box 2, case 2). In addition, factors associated with response and non-response are investigated.

Finally, in Chapter 6, the main findings of this thesis are summarized and discussed, and implications for clinical practice and future research are provided.

Box 2. Case descriptions

Case 1

A 55-year-old woman sustained a first-ever ischemic stroke in the left hemisphere. Prior to her stroke, she was a healthy store employee with an active lifestyle. She started inpatient rehabilitation seven days after stroke because of a right-sided hemiparesis. Her body awareness and visuospatial function were normal, nor were there impairments of attention, memory or language. At the time of inclusion in our robotic training study (i.e., the *LOPES-Arts study*), she was 23 days post stroke, at which time she had a lower-extremity Fugl-Meyer motor score 21 over 34 (with higher scores indicating better level of motor recovery). Indoors, she walked short distances with a walker, and she was able to take a few steps under supervision from a physical therapist without the use of a walking aid. She used a wheelchair for outdoor mobility. Her gait pattern showed reduced paretic knee stability in the stance phase together with increased lateral trunk movements and reduced paretic arm swing. After randomization, she started robotic gait training in the LOPES II with a focus on improving paretic knee stability during the stance phase.

Case 2

A 58-year-old man sustained a first-ever ischemic right-hemisphere stroke presenting with poor balance and left-sided hemiparesis. Prior to his stroke, he worked as an office manager and liked to spend time with his family and friends. After his stroke, he received three months of inpatient rehabilitation, followed by a 10-week outpatient rehabilitation period. His therapy focused on improving visuospatial neglect, muscle strength and coordination of the left leg and arm, as well as on improving balance and coordination during standing and walking. At the time of inclusion in our robotic gait training study (i.e., the *I-PICS-study*), 14 months after stroke, he walked indoors without a walking aid, whereas he used a cane while walking in the community. He showed a lower extremity Fugl-Meyer motor score 24 over 34 (with higher scores indicating better level of motor recovery). He was able to raise both heels from the floor during bilateral stance, but not during unilateral standing on his paretic leg. Gait analysis revealed a clear asymmetry in propulsion in favor of the non-paretic leg. Given the potential to improve his propulsion symmetry, he was admitted to the robotic gait training in LOPES II.

References

1. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(5):439-458.
2. WHO MONICA Project Investigators. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. J Clin Epidemiol. 1988;41(2):105-114.
3. Truelsen T, Begg S, Mathers C. The Global Burden of Cerebrovascular Disease. Geneve, World Health Organization; 2006. https://www.who.int/healthinfo/statistics/bod_cerebrovasculardiseasestroke.pdf. Accessed, December 11, 2020.
4. Grysiewicz RA, Thomas K, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. Neurol Clin. 2008;26(4):871-895.
5. Menezes NM, Ay H, Wang Zhu M, et al. The real estate factor: quantifying the impact of infarct location on stroke severity. Stroke. 2007;38(1):194-197.
6. Adams RW, Gandevia SC, Skuse NF. The distribution of muscle weakness in upper motoneuron lesions affecting the lower limb. Brain. 1990;113(5):1459-1476.
7. Baker SN, Zaaimi B, Fisher KM, Edgley SA, Soteropoulos DS. Pathways mediating functional recovery. Prog Brain Res. 2015;218:389-412.
8. Bonita R, Beaglehole R. Recovery of motor function after stroke. Stroke. 1988;19(12):1497-1500.
9. Good DC, Bettermann K, Reichwein RK. Stroke rehabilitation. Continuum. 2011;17(3):545-567.
10. Horn SD, DeJong G, Smout RJ, Gassaway J, James R, Conroy B. Stroke rehabilitation patients, practice, and outcomes: is earlier and more aggressive therapy better? Arch Phys Med Rehabil. 2005;86(12):101-114.
11. Kwakkel G, Kollen B, Twisk J. Impact of time on improvement of outcome after stroke. Stroke. 2006;37(9):2348-2353.
12. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. Lancet. 2011;377(9778):1693-1702.
13. Bernhardt J, Hayward KS, Kwakkel G, et al. Agreed Definitions and a Shared Vision for New Standards in Stroke Recovery Research: The Stroke Recovery and Rehabilitation Roundtable Taskforce. Neurorehabil Neural Repair. 2017;31(9):793-799.
14. Buma F, Kwakkel G, Ramsey N. Understanding upper limb recovery after stroke. Restor Neurol Neurosci. 2013;31(6):707-722.
15. Taub E. Movement in nonhuman primates deprived of somatosensory feedback. Exerc Sport Sci Rev. 1976;4:335-374.
16. Taub E, Uswatte G, Mark VW, Morris DM. The learned nonuse phenomenon: implications for rehabilitation. Eura Medicophys. 2006;42(3):241-256.
17. Ballester BR, Maier M, San Segundo Mozo RM, Castañeda V, Duff A, PF MJV. Counteracting learned non-use in chronic stroke patients with reinforcement-induced movement therapy. J Neuroeng Rehabil. 2016;13(1):74.
18. Liu XH, Huai J, Gao J, Zhang Y, Yue SW. Constraint-induced movement therapy in treatment of acute and sub-acute stroke: a meta-analysis of 16 randomized controlled trials. Neural Regen Res. 2017;12(9):1443-1450.
19. Wolf SL, Blanton S, Baer H, Breshears J, Butler AJ. Repetitive task practice: a critical review of constraint-induced movement therapy in stroke. Neurologist. 2002;8(6):325-338.
20. Hase K, Suzuki E, Matsumoto M, Fujiwara T, Liu MG. Effects of Therapeutic Gait Training Using a Prosthesis and a Treadmill for Ambulatory Patients With Hemiparesis. Arch Phys Med Rehabil. 2011;92(12):1961-1966.
21. Kim NH, Cha YJ. Effect of gait training with constrained-induced movement therapy (CIMT) on the balance of stroke patients. J Phys Ther Sci. 2015;27(3):611-613.

22. Olney SJ, Richards C. Hemiparetic gait following stroke. Part I: Characteristics. Gait Posture. 1996;4(2):136-148.
23. Wade DT, Hewer RL. Functional abilities after stroke: measurement, natural history and prognosis. J Neurol Neurosurg Psychiatry. 1987;50(2):177-182.
24. Duncan PW, Zorowitz R, Bates B, et al. Management of Adult Stroke Rehabilitation Care: a clinical practice guideline. Stroke. 2005;36(9):100-143.
25. Cho KH, Lee JY, Lee KJ, Kang EK. Factors Related to Gait Function in Post-stroke Patients. J Phys Ther Sci. 2014;26(12):1941-1944.
26. Schmid A, Duncan PW, Studenski S, et al. Improvements in speed-based gait classifications are meaningful. Stroke. 2007;38(7):2096-2100.
27. Bohannon RW, Andrews AW, Smith MB. Rehabilitation goals of patients with hemiplegia. Int J Rehabil Res. 1988;11(2):181-184.
28. Harris JE, Eng JJ. Goal Priorities Identified through Client-Centred Measurement in Individuals with Chronic Stroke. Physiother Can. 2004;56(3):171-176.
29. Hornby TG, Reisman DS, Ward IG, et al. Clinical Practice Guideline to Improve Locomotor Function Following Chronic Stroke, Incomplete Spinal Cord Injury, and Brain Injury. J Neurol Phys Ther. 2020;44(1):49-100.
30. Van Duijnhoven HJR. The challenges of dynamic balance and gait for people after stroke. Enschede, Radboud University; 2019.
31. Collen FM, Wade DT, Bradshaw CM. Mobility after stroke: reliability of measures of impairment and disability. Int Disabil Stud. 1990;12(1):6-9.
32. Mehrholz J, Wagner K, Rutte K, Meissner D, Pohl M. Predictive validity and responsiveness of the functional ambulation category in hemiparetic patients after stroke. Arch Phys Med Rehabil. 2007;88(10):1314-1319.
33. Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1995;76(1):27-32.
34. Skilbeck CE, Wade DT, Hewer RL, Wood VA. Recovery after stroke. J Neurol Neurosurg Psychiatry. 1983;46(1):5-8.
35. Kollen B, van de Port I, Lindeman E, Twisk J, Kwakkel G. Predicting improvement in gait after stroke: a longitudinal prospective study. Stroke. 2005;36(12):2676-2680.
36. Veerbeek JM, Van Wegen EE, Harmeling-Van der Wel BC, Kwakkel G. Is accurate prediction of gait in nonambulatory stroke patients possible within 72 hours poststroke? The EPOS study. Neurorehabil Neural Repair. 2011;25(3):268-274.
37. Verheyden G, Nieuwboer A, De Wit L, et al. Trunk performance after stroke: an eye catching predictor of functional outcome. J Neurol Neurosurg Psychiatry. 2007;78(7):694-698.
38. Gage JR. Gait analysis. An essential tool in the treatment of cerebral palsy. Clin Orthop Relat Res. 1993(288):126-134.
39. Balasubramanian CK, Bowden MG, Neptune RR, Kautz SA. Relationship between step length asymmetry and walking performance in subjects with chronic hemiparesis. Arch Phys Med Rehabil. 2007;88(1):43-49.
40. Chen G, Patten C, Kothari DH, Zajac FE. Gait differences between individuals with post-stroke hemiparesis and non-disabled controls at matched speeds. Gait Posture. 2005;22(1):51-56.
41. Patterson KK, Parafianowicz I, Danells CJ, et al. Gait asymmetry in community-ambulating stroke survivors. Arch Phys Med Rehabil. 2008;89(2):304-310.
42. Hsiao H, Higginson JS, Binder-Macleod SA. Baseline predictors of treatment gains in peak propulsive force in individuals poststroke. J Neuroeng Rehabil. 2016;13:2.
43. Patterson KK, Nadkarni NK, Black SE, McIlroy WE. Gait symmetry and velocity differ in their relationship to age. Gait Posture. 2012;35(4):590-594.

44. Moseley A, Wales A, Herbert R, Schurr K, Moore S. Observation and analysis of hemiplegic gait: stance phase. Aust J Physiother. 1993;39(4):259-267.
45. Campanini I, Merlo A, Damiano B. A method to differentiate the causes of stiff-knee gait in stroke patients. Gait Posture. 2013;38(2):165-169.
46. Balaban B, Tok F. Gait disturbances in patients with stroke. PMR. 2014;6(7):635-642.
47. Bowden MG, Balasubramanian CK, Neptune RR, Kautz SA. Anterior-posterior ground reaction forces as a measure of paretic leg contribution in hemiparetic walking. Stroke. 2006;37(3):872-876.
48. Awad LN, Binder-Macleod SA, Pohlig RT, Reisman DS. Paretic Propulsion and Trailing Limb Angle Are Key Determinants of Long-Distance Walking Function After Stroke. Neurorehabil Neural Repair. 2015;29(6):499-508.
49. Roelker SA, Bowden MG, Kautz SA, Neptune RR. Paretic propulsion as a measure of walking performance and functional motor recovery post-stroke: A review. Gait Posture. 2019;68:6-14.
50. Knutsson E, Richards C. Different types of disturbed motor control in gait of hemiparetic patients. Brain. 1979;102(2):405-430.
51. Lehmann JF, Condon SM, Price R, deLateur BJ. Gait abnormalities in hemiplegia: their correction by ankle-foot orthoses. Arch Phys Med Rehabil. 1987;68(11):763-771.
52. Nadeau S, Gravel D, Arsenault AB, Bourbonnais D. Plantarflexor weakness as a limiting factor of gait speed in stroke subjects and the compensating role of hip flexors. Clin Biomech. 1999;14(2):125-135.
53. Teixeira-Salmela LF, Nadeau S, McBride I, Olney SJ. Effects of muscle strengthening and physical conditioning training on temporal, kinematic and kinetic variables during gait in chronic stroke survivors. J Rehabil Med. 2001;33(2):53-60.
54. Allen JL, Kautz SA, Neptune RR. Step length asymmetry is representative of compensatory mechanisms used in post-stroke hemiparetic walking. Gait Posture. 2011;33(4):538-543.
55. Lewek MD, Osborn AJ, Wutzke CJ. The influence of mechanically and physiologically imposed stiff-knee gait patterns on the energy cost of walking. Arch Phys Med Rehabil. 2012;93(1):123-128.
56. Wrisley DM, Marchetti GF, Kuharsky DK, Whitney SL. Reliability, internal consistency, and validity of data obtained with the functional gait assessment. Phys Ther. 2004;84(10):906-918.
57. Liaw LJ, Hsieh CL, Lo SK, Lee S, Huang MH, Lin JH. Psychometric properties of the modified Emory Functional Ambulation Profile in stroke patients. Clin Rehabil. 2006;20(5):429-437.
58. Houdijk H, van Ooijen MW, Kraal JJ, et al. Assessing gait adaptability in people with a unilateral amputation on an instrumented treadmill with a projected visual context. Phys Ther. 2012;92(11):1452-1460.
59. Geerse DJ, Roerdink M, Marinus J, van Hilten JJ. Assessing walking adaptability in stroke patients. Disabil Rehabil. 2020:1-9.
60. Den Otter AR, Geurts AC, de Haart M, Mulder T, Duysens J. Step characteristics during obstacle avoidance in hemiplegic stroke. Exp Brain Res. 2005;161(2):180-192.
61. Said CM, Goldie PA, Culham E, Sparrow WA, Patla AE, Morris ME. Control of lead and trail limbs during obstacle crossing following stroke. Phys Ther. 2005;85(5):413-427.
62. Smulders K, van Swigchem R, de Swart BJ, Geurts AC, Weerdesteyn V. Community-dwelling people with chronic stroke need disproportionate attention while walking and negotiating obstacles. Gait Posture. 2012;36(1):127-132.
63. Guzik A, Drużbicki M, Wolan-Nieroda A. Assessment of two gait training models: conventional physical therapy and treadmill exercise, in terms of their effectiveness after stroke. Hippokratia. 2018;22(2):51-59.
64. Pontes SS, de Carvalho ALR, Almeida KO, et al. Effects of isokinetic muscle strengthening on muscle strength, mobility, and gait in post-stroke patients: a systematic review and meta-analysis. Clin Rehabil. 2019;33(3):381-394.
65. Saunders DH, Sanderson M, Hayes S, et al. Physical fitness training for stroke patients. Cochrane Database Syst Rev. 2020;3(3):CD003316.
66. Mehrholz J, Thomas S, Elsner B. Treadmill training and body weight support for walking after stroke. Cochrane Database Syst Rev. 2017;8(8):CD002840.
67. Busk H, Stausholm MB, Lykke L, Wienecke T. Electrical Stimulation in Lower Limb During Exercise to Improve Gait Speed and Functional Motor Ability 6 Months Poststroke. A Review with Meta-Analysis. J Stroke Cerebrovasc Dis. 2020;29(3):104565.
68. Kafri M, Laufer Y. Therapeutic effects of functional electrical stimulation on gait in individuals post-stroke. Ann Biomed Eng. 2015;43(2):451-466.
69. Woodford H, Price C. EMG biofeedback for the recovery of motor function after stroke. Cochrane Database Syst Rev. 2007(2):CD004585.
70. Zijlstra A, Mancini M, Chiari L, Zijlstra W. Biofeedback for training balance and mobility tasks in older populations: a systematic review. J Neuroeng Rehabil. 2010;7:58.
71. Veerbeek JM, van Wegen E, van Peppen R, et al. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. PLoS One. 2014;9(2):87987.
72. Maier M, Ballester BR, Verschure P. Principles of Neurorehabilitation After Stroke Based on Motor Learning and Brain Plasticity Mechanisms. Front Syst Neurosci. 2019;13:74.
73. Bayona NA, Bitensky J, Teasell R. Plasticity and reorganization of the uninjured brain. Top Stroke Rehabil. 2005;12(3):1-10.
74. Carr J, Shepherd R. Neurological rehabilitation: optimizing motor performance. Oxford: Butterworth Heinemann; 1998.
75. Brunelli S, Iosa M, Fusco FR, et al. Early body weight-supported overground walking training in patients with stroke in subacute phase compared to conventional physiotherapy: a randomized controlled pilot study. Int J Rehabil Res. 2019;42(4):309-315.
76. Franceschini M, Carda S, Agosti M, Antenucci R, Malgrati D, Cisari C. Walking after stroke: what does treadmill training with body weight support add to overground gait training in patients early after stroke?: a single-blind, randomized, controlled trial. Stroke. 2009;40(9):3079-3085.
77. States RA, Pappas E, Salem Y. Overground physical therapy gait training for chronic stroke patients with mobility deficits. Cochrane Database Syst Rev. 2009;3:CD006075.
78. Buurke JH, Nene AV, Kwakkel G, Erren-Wolters V, Ijzerman MJ, Hermens HJ. Recovery of gait after stroke: what changes? Neurorehabil Neural Repair. 2008;22(6):676-683.
79. Den Otter AR, Geurts AC, Mulder T, Duysens J. Gait recovery is not associated with changes in the temporal patterning of muscle activity during treadmill walking in patients with post-stroke hemiparesis. Clin Neurophysiol. 2006;117(1):4-15.
80. Kuys SS, Brauer SG, Ada L. Higher-intensity treadmill walking during rehabilitation after stroke in feasible and not detrimental to walking pattern or quality: a pilot randomized trial. Clin Rehabil. 2011;25(4):316-326.
81. Lennon S, Ashburn A, Baxter D. Gait outcome following outpatient physiotherapy based on the Bobath concept in people post stroke. Disabil Rehabil. 2006;28(14):873-881.
82. Mao YR, Lo WL, Lin Q, et al. The Effect of Body Weight Support Treadmill Training on Gait Recovery, Proximal Lower Limb Motor Pattern, and Balance in Patients with Subacute Stroke. Biomed Res Int. 2015;2015:175719.
83. Yavuzer G, Eser F, Karakus D, Karaoglan B, Stam HJ. The effects of balance training on gait late after stroke: a randomized controlled trial. Clin Rehabil. 2006;20(11):960-969.
84. Holder NL, Clark HA, DiBlasio JM, et al. Cause, prevalence, and response to occupational musculoskeletal injuries reported by physical therapists and physical therapist assistants. Phys Ther. 1999;79(7):642-652.
85. Schmidt H, Werner C, Bernhardt R, Hesse S, Krüger J. Gait rehabilitation machines based on programmable footplates. J Neuroeng Rehabil. 2007;4:2.

86. Hidler J, Nichols D, Pelliccio M, et al. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair. 2009;23(1):5-13.
87. Veneman JF, Menger J, van Asseldonk EH, van der Helm FC, van der Kooij H. Fixating the pelvis in the horizontal plane affects gait characteristics. Gait Posture. 2008;28(1):157-163.
88. Colombo G, Joerg M, Schreier R, Dietz V. Treadmill training of paraplegic patients using a robotic orthosis. J Rehabil Res Dev. 2000;37(6):693-700.
89. West RG, Inventor; HealthSouth Corporation, Assignee. Powered gait orthosis and method of utilizing same. US6689075B2. February 10, 2004.
90. Banala SK, Kim SH, Agrawal SK, Scholz JP. Robot assisted gait training with active leg exoskeleton (ALEX). IEEE Trans Neural Syst Rehabil Eng. 2009;17(1):2-8.
91. Meuleman J, van Asseldonk E, van Oort G, Rietman H, van der Kooij H. LOPES II--Design and Evaluation of an Admittance Controlled Gait Training Robot With Shadow-Leg Approach. IEEE Trans Neural Syst Rehabil Eng. 2016;24(3):352-363.
92. Zanotto D, Stegall P, Agrawal SK. Adaptive assist-as-needed controller to improve gait symmetry in robot-assisted gait training. IEEE Int Conf Robot Automat. 2014; 2014.
93. Hidler J, Wisman W, Neckel N. Kinematic trajectories while walking within the Lokomat robotic gait-orthosis. Clin Biomech. 2008;23(10):1251-1259.
94. Reinkensmeyer DJ, Akoner O, Ferris DP, Gordon KE. Slacking by the human motor system: computational models and implications for robotic orthoses. Annu Int Conf IEEE Eng Med Biol Soc. 2009;2009:2129-2132.
95. van Kammen K, Boonstra AM, van der Woude LHV, Visscher C, Reinders-Messelink HA, den Otter R. Lokomat guided gait in hemiparetic stroke patients: the effects of training parameters on muscle activity and temporal symmetry. Disabil Rehabil. 2020;42(21):2977-2985.
96. Cano-de-la-Cuerda R, Molero-Sánchez A, Carratalá-Tejada M, et al. Theories and control models and motor learning: clinical applications in neuro-rehabilitation. Neurologia. 2015;30(1):32-41.
97. Dhawale AK, Smith MA, Ölveczky BP. The Role of Variability in Motor Learning. Annu Rev Neurosci. 2017;40:479-498.
98. Tefertiller C, Pharo B, Evans N, Winchester P. Efficacy of rehabilitation robotics for walking training in neurological disorders: a review. J Rehabil Res Dev. 2011;48(4):387-416.
99. Hussain S, Xie SQ, Liu G. Robot assisted treadmill training: mechanisms and training strategies. Med Eng Phys. 2011;33(5):527-533.
100. Veneman JF, Kruidhof R, Hekman EE, Ekkelenkamp R, Van Asseldonk EH, van der Kooij H. Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):379-386.
101. Aurich-Schuler T, Gut A, Labruyère R. The FreeD module for the Lokomat facilitates a physiological movement pattern in healthy people - a proof of concept study. J Neuroeng Rehabil. 2019;16(1):26.
102. Duschau-Wicke A, von Zitzewitz J, Caprez A, Lunenburger L, Riener R. Path control: a method for patient-cooperative robot-aided gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2010;18(1):38-48.
103. Emken JL, Bobrow JE, Reinkensmeyer DJ. Robotic movement training as an optimization problem: designing a controller that assists only as needed. Int Conf Rehabil Robot. 2005, 2005.
104. Chen G, Ye J, Liu Q, et al. Adaptive Control Strategy for Gait Rehabilitation Robot to Assist-When-Needed. IEEE Int Conf Real-time Comp Robot. 2018, 2018.
105. Duschau-Wicke A, Caprez A, Riener R. Patient-cooperative control increases active participation of individuals with SCI during robot-aided gait training. J Neuroeng Rehabil. 2010;7:43.
106. Emken JL, Benitez R, Reinkensmeyer DJ. Human-robot cooperative movement training: learning a novel sensory motor transformation during walking with robotic assistance-as-needed. J Neuroeng Rehabil. 2007;4:8.
107. Fleerkotte BM, Koopman B, Buurke JH, van Asseldonk EH, van der Kooij H, Rietman JS. The effect of impedance-controlled robotic gait training on walking ability and quality in individuals with chronic incomplete spinal cord injury: an explorative study. J Neuroeng Rehabil. 2014;11:26.
108. Koopman B, van Asseldonk EH, van der Kooij H. Selective control of gait subtasks in robotic gait training: foot clearance support in stroke survivors with a powered exoskeleton. J Neuroeng Rehabil. 2013;10:3.
109. Meuleman J. Design of a robot-assisted gait trainer: LOPES II. Enschede, University of Twente; 2015.
110. Asl HJ, Yoon J. Stable assist-as-needed controller design for a planar cable-driven robotic system. Int J Control Autom Syst. 2017;15(6):2871-2882.
111. Riener R, Lünenburger L, Maier IC, Colombo G, Dietz V. Locomotor Training in Subjects with Sensori-Motor Deficits: An Overview of the Robotic Gait Orthosis Lokomat. J Health Eng. 2010;1:517674.
112. Cao JH, Xie SQ, Das R, Zhu GL. Control strategies for effective robot assisted gait rehabilitation: The state of art and future prospects. Med Eng Phys. 2014;36(12):1555-1566.
113. Pennycott A, Wyss D, Vallery H, Klamroth-Marganska V, Riener R. Towards more effective robotic gait training for stroke rehabilitation: a review. J Neuroeng Rehabil. 2012;9:65.
114. Cho JE, Yoo JS, Kim KE, et al. Systematic Review of Appropriate Robotic Intervention for Gait Function in Subacute Stroke Patients. Biomed Res Int. 2018;2018:4085298.
115. Bruni MF, Melegari C, De Cola MC, Bramanti A, Bramanti P, Calabrò RS. What does best evidence tell us about robotic gait rehabilitation in stroke patients: A systematic review and meta-analysis. J Clin Neurosci. 2018;48:11-17.
116. Mehrholz J, Thomas S, Kugler J, Pohl M, Elsner B. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2020;10:CD006185.
117. Moucheboeuf G, Griffier R, Gasq D, et al. Effects of robotic gait training after stroke: A meta-analysis. Ann Phys Rehabil Med. 2020;63(6):518-534.
118. Hornby TG, Campbell DD, Kahn JH, Demott T, Moore JL, Roth HR. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. Stroke. 2008;39(6):1786-1792.
119. Forrester LW, Roy A, Krebs HI, Macko RF. Ankle training with a robotic device improves hemiparetic gait after a stroke. Neurorehabil Neural Repair. 2011;25(4):369-377.
120. Forrester LW, Roy A, Krywonis A, Kehs G, Krebs HI, Macko RF. Modular ankle robotics training in early subacute stroke: a randomized controlled pilot study. Neurorehabil Neural Repair. 2014;28(7):678-687.
121. Forrester LW, Roy A, Hafer-Macko C, Krebs HI, Macko RF. Task-specific ankle robotics gait training after stroke: a randomized pilot study. J Neuroeng Rehabil. 2016;13(1):51.
122. Seo JS, Yang HS, Jung S, Kang CS, Jang S, Kim DH. Effect of reducing assistance during robot-assisted gait training on step length asymmetry in patients with hemiplegic stroke: A randomized controlled pilot trial. Medicine. 2018;97(33):11792.
123. De Luca A, Vernetti H, Capra C, et al. Recovery and compensation after robotic assisted gait training in chronic stroke survivors. Disabil Rehabil Assist Technol. 2019;14(8):826-838.
124. Srivastava S, Kao PC, Kim SH, et al. Assist-as-Needed Robot-Aided Gait Training Improves Walking Function in Individuals Following Stroke. IEEE Trans Neural Syst Rehabil Eng. 2015;23(6):956-963.
125. Srivastava S, Kao PC, Reisman DS, Scholz JP, Agrawal SK, Higginson JS. Robotic Assist-As-Needed as an Alternative to Therapist-Assisted Gait Rehabilitation. Int J Phys Med Rehabil. 2016;4(5):370.
126. Krishnan C, Ranganathan R, Kantak SS, Dhaher YY, Rymer WZ. Active robotic training improves locomotor function in a stroke survivor. J Neuroeng Rehabil. 2012;9:57.

Chapter 2

Immediate after-effects of robot-assisted gait with pelvic support or pelvic constraint on overground walking in healthy subjects

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Abstract

Background

Recovery of walking is a primary rehabilitation goal of most stroke survivors. Control of pelvic movements is one of the essential determinants of gait, yet surprisingly, conventional robot-assisted gait trainers constrain pelvic movements. Novel robot-assisted gait trainers, such as LOPES II, are able to support pelvic movements during gait. The aim of this cross-over study was to investigate the immediate after-effects of pelvic support (PS) or pelvic constraint (PC) gait training with LOPES II on overground walking in healthy subjects.

Methods

Thirteen able-bodied subjects (22.8±2.1 years) participated in two 20-minute gait training sessions with LOPES II; one with PS and one with PC. During the PS-training, the LOPES II actively guided the lateral displacement of the pelvis, while pelvic rotations were free. During the PC-condition, both lateral displacement and pelvic rotations were constrained and reduced to a minimum. The training sessions were separated by a 30-minute resting period. Lateral displacement of the pelvis, hip and knee kinematics, and spatiotemporal parameters during overground walking were determined at baseline and immediately following the training using 3D-gait analysis.

Results

During the PS-condition in LOPES II the lateral pelvic displacement was significantly greater (105.6 ± 0.5 mm) than during the PC-condition (10.8 ± 0.7 mm; $p < 0.001$). Analysis of the first five steps of overground walking immediately following PC-condition showed significantly smaller lateral displacements of the pelvis (32.3 ± 12.0 mm) compared to PS-condition (40.1 ± 9.8 mm; $p < 0.01$). During the first five steps, step width was significantly smaller after PC-condition (0.17 ± 0.04 m) compared to PS-condition (0.20 ± 0.04 m; $p = 0.01$) and baseline (0.19 ± 0.03 m; $p = 0.01$). Lateral displacement of the pelvis and step width post training returned to baseline levels within 10 steps. PC- nor PS-condition affected kinematics, gait velocity, cadence, stride length or stance time.

Conclusions

In healthy subjects, robot-assisted gait training with pelvic constraint had immediate negative after-effects on the overground walking pattern, as compared to robot-assisted gait training with pelvic support. Gait training including support of the lateral displacement of the pelvis better resembles the natural gait pattern. It remains to be identified whether pelvic support during robot-assisted gait training is superior to pelvic constraint to promote gait recovery in individuals with neurological disorders.

Introduction

Recovery of walking is an important rehabilitation goal for many stroke survivors[1]. Although many individuals after stroke regain some degree of walking capacity, the hemiparetic gait pattern is commonly characterized by spatiotemporal asymmetry, reduced walking speed, and impaired balance control[2,3]. Furthermore, hemiparetic gait is associated with atypical pelvic movements[4]. Since control of pelvic movements is one of the essential determinants of gait[5], restoring the normal pelvic movement pattern seems a crucial target for gait training after stroke. Nowadays, robotic gait trainers are increasingly used for the rehabilitation of stroke survivors[6], as well as individuals with spinal cord injury[7] or cerebral palsy[8]. First-generation robotic gait trainers used for the rehabilitation of these individuals, however, generally impose restrictions to both lateral translations and rotations of the pelvis.

Restriction of pelvic movements imposed by a robotic gait trainer substantially influences the gait pattern. Indeed, in healthy adults, walking with restrictions of both lateral pelvic translations and rotations may result in narrower step width and excessive trunk rotations[9], shorter[10] or longer step length[9] and reduced range of motion of the lower limb joints[10]. In addition, restrictions of pelvic movements may yield increased activation of the adductor longus muscle[11], whereas no effect on gluteus medius activity was observed during stance[10,11]. Furthermore, reduced pelvic range of motion during treadmill walking was shown to be retained during unconstrained treadmill walking[12]. These observations raise the question whether these adverse effects of restricted pelvic movements during robotic gait training might be transferred to unconstrained overground walking after robotic gait training. If such effects would occur, robotic gait training involving restricted pelvic movements might even be detrimental for relearning an optimal gait pattern after stroke. Conversely, adding degrees of freedom to the pelvis might enable patients to adopt a more normal gait pattern while walking in a robotic gait trainer[11]. Newly developed robotic gait trainers like the lower extremity powered exoskeleton LOPES[13,14] and the latest version of the Lokomat (Lokomat Free-D module) allow more degrees of freedom at the pelvic level. In addition, some of these new generation robotic gait trainers can provide support of pelvic movements tailored to the individual patient's need.

Although support of pelvic movements has the potential to improve the gait pattern during robotic gait training and its effect was shown to be retained during unconstrained treadmill walking[12], the immediate after-effects of either pelvic support or pelvic constraint on the unconstrained, overground gait pattern have not yet been studied. As overground walking more closely resembles walking in daily life than treadmill walking does, investigating the transfer of these pelvic conditions to overground walking is important. Therefore, the aim of the current study was to investigate the immediate after-effects of robot-assisted gait with either pelvic constraint or pelvic support on the first meters of overground walking in healthy subjects, thereby resembling the training conditions in the first-generation and new generation robotic gait trainers, respectively. Furthermore, the overground gait pattern after robot-assisted gait with pelvic constraint or pelvic support was compared with the normal overground gait pattern. It was hypothesized that restricting pelvic movements during robot-assisted gait would lead to reduced lateral pelvic translations during overground walking compared to robot-assisted gait with pelvic support and normal overground walking. Robot-assisted gait with pelvic support was expected to more closely resemble the lateral pelvic displacements of normal gait.

Methods

Participants

From April 2014 to July 2014 a total number of 14 healthy young adults were recruited in Nijmegen, the Netherlands, to participate in this study. Participants did not suffer from any injury or impairment interfering with balance and gait. All participants gave written informed consent. The study was designed following the Declaration of Helsinki. The study protocol (NL 42426.044.12) was approved by the Medical Ethical Committee Twente (Enschede, the Netherlands).

Design

Participants were enrolled in a cross-over study, including two 20-minute walking conditions in the robotic gait trainer LOPES II with either pelvic support (PS) or pelvic constraint (PC). Each LOPES II condition was preceded and followed by an overground 3D-gait analysis (Figure 1).

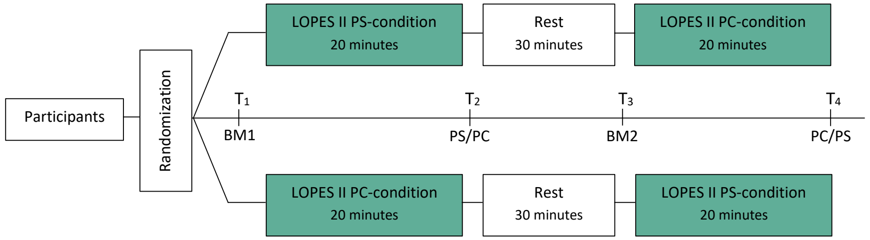

Figure 1. Study design. Before and after the 20-minute walk in LOPES II a 3D-gait analysis was performed (baseline measurement 1 (BM1), baseline measurement 2 (BM2), pelvic support (PS), pelvic constraint (PC)).

Materials

Robotic gait trainer

The LOPES II is a robotic gait trainer, combined with a treadmill and body weight support system (Figure 2). LOPES II has eight powered degrees of freedom, actuating knee flexion/extension, hip flexion/extension, hip adduction/abduction, and pelvic translations in the lateral and anterior/posterior directions. In addition, the robot allows free motion of pelvic rotations, hip and foot endorotation/exorotation, and ankle plantarflexion/dorsiflexion and inversion/eversion. Together, its settings allow pelvic movements to be either supported or mechanically constrained. The level of support is adjusted for each individual, as LOPES II controls the interaction forces during gait training. The applied forces are calculated from the deviation of the actual movement from the predefined gait trajectory, and the set level of guidance force. The level of guidance force can be set in two parts: the general guidance force level is set for all subtasks of walking, and on top of that the specific guidance force level can be adjusted for each specific gait subtask, such as 'weight shift guidance'. Together, LOPES II applies joint torques to re-direct the deviations in pelvis and limb movements from the participant's gait trajectory towards the predefined, desired gait trajectory. The applied predefined gait trajectories are derived from the gait pattern of healthy walkers and adjusted to the individual's walking velocity and participant's height. For a detailed description of the LOPES II and its control we refer to a publication by Meuleman et al[14].

Figure 2. Robotic gait trainer LOPES II.

The general guidance force and lateral translations and rotations of the pelvis varied between the two LOPES II conditions. During the PS-condition the lateral pelvic translations were guided towards the imposed pre-defined trajectory (low level of general guidance: 15 Nm/rad; high level of weight shift guidance: 20 N/mm; large weight shift amplitude: 53 mm), while pelvic rotations were left free. During the PC-condition both the lateral pelvic translations and pelvic rotations were constrained, reducing the participants' pelvic movements to a minimum (high level of general guidance: 1500 Nm/rad; high level of weight shift guidance: 20 N/mm; small weight shift amplitude: 5.3 mm). Figure 3 shows the imposed and actual pelvic movements while walking in LOPES II during both the PS- and PC-conditions. During the PS- and PC-condition, the LOPES II recorded pelvic position, segment angles (for calculating kinematics), spatiotemporal gait parameters and interaction forces between the robot and the participant (f_s = 100 Hz). Participants walked at a standardized gait speed of 0.55 m/s, a speed that is also used during robotic gait in our ongoing intervention study in people in the subacute phase after stroke. Body weight support was set at 10% of the total body mass to carry the load of the system.

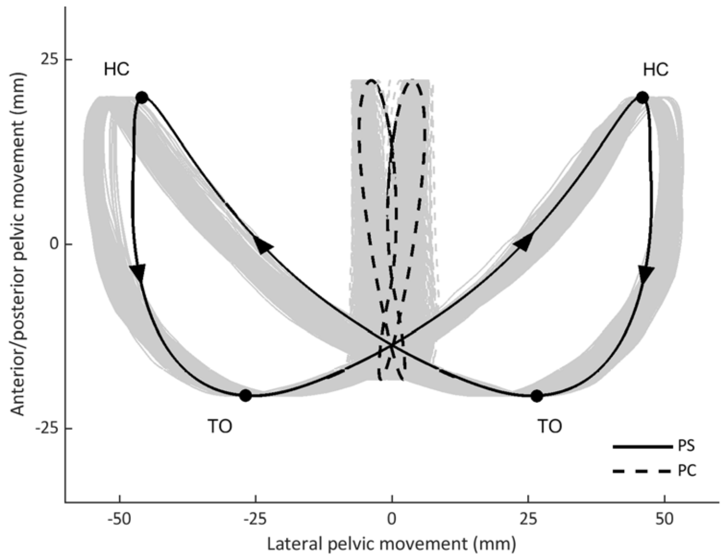

Figure 3. Typical example of imposed (black line) and actual (grey line) pelvic movements in the transverse plane (X-Y) during gait in LOPES II for the pelvic support (PS) and pelvic constraint (PC) conditions. Pelvic position was determined by the midpoint between the hip joints. The pelvic movements were corrected for the displacement in the line of progression. Arrows indicate the direction of the pelvic displacements. The markers represent the moment of heel contact (HC) and toe off (TO).

3D-gait analysis

To assess the immediate after-effect of the LOPES II condition on the overground gait pattern, a 3D-gait analysis was performed before and immediately after each LOPES II condition. Twenty reflective markers (14 mm) were attached to the participants' skin, according to the Plug-In-Gait Lower body model (Plug-in-Gait, Vicon Motion Systems Ltd, Oxford, UK). Marker positions were indicated on the skin to ensure fast and equal marker placement across the gait analyses. The position of the reflective markers was registered by ten infrared cameras (f_s = 100 Hz; Vicon mX 1.7.1, Oxford Metrics, UK). Participants walked at a self-selected comfortable speed across a 6-meter walkway. A single walk across the walkway was defined as a trial. A total of five trials were collected for each participant at every gait assessment, recording at least five steps walked within the capture volume per trial.

Procedure

A 3D-gait analysis (Baseline Measurement 1) was performed at the start of the experiment to determine the overground gait pattern (T1). Participants were then installed in LOPES II and completed a 20-minute walking condition with either supported or constrained pelvic movements. Participants walked without handrail support and were instructed to follow the pre-defined trajectory of the LOPES II. After completing a LOPES II condition, participants were transferred to the gait laboratory in a wheelchair to ensure no more than 3 steps of walking before the start of the second gait analysis. The reflective markers were reattached to the skin and a new analysis was performed within 5 minutes after the end of the LOPES II condition (T2). After completing this second 3D-gait analysis a 30-minute break was allowed. Thereafter, the procedure was repeated for the second LOPES II condition, yielding Baseline Measurement 2 (T3) followed by the fourth 3D-gait analysis (T4).

Data analysis

Data collected by LOPES II was used to determine the kinematics and spatiotemporal gait parameters during the last 40 strides of walking in the PC- and PS-conditions. To determine participant's final level of adaptation to the applied condition, the root mean square (RMS) of the interaction forces in the mediolateral direction at the pelvis were calculated for the last 40 strides of walking in each condition in LOPES II. The Vicon Plug-In-Gait model and software were used to calculate the kinematics and spatiotemporal gait parameters for each trial of the 3D-gait analysis. Data was further analyzed using custom-written software (MATLAB, Mathworks Inc., Natick, MA, USA). The lateral pelvic displacement (LPD) during robot-assisted gait and unsupported overground walking was defined as the absolute peak-to-peak displacement (mm) of the pelvis perpendicular to the walking direction during each stride. In addition, we determined range of motion of the knee and hip joint in the sagittal plane and spatiotemporal parameters including stance time (%), stride length (m), step width (m), gait velocity (m/s), and cadence (steps/min). Average values were calculated for all variables per trial.

Statistics

The statistical analysis was performed using Stata software (TX StataCorp LP 2013, version 13). The normal distribution of the LPD, interaction forces, spatiotemporal parameters, and kinematics was tested using a Shapiro-Wilk test. Thereafter, two-sided paired-samples t-test were performed to examine differences in LPD, interaction forces, spatiotemporal parameters, and kinematics *during* gait in LOPES II between the last 40 strides of walking in the PS- and PC-conditions. Next, one-way repeated measures analyses of variance with 'Condition' (PS-condition, PC-condition, and Baseline Measurement) as within-subjects factor were performed to determine differences in LPD, spatiotemporal parameters, and kinematics for the first trial of overground walking immediately *after* the PS- and PC-condition. Since no significant differences were found between the LPD, spatiotemporal parameters, or kinematics of Baseline Measurements 1 and 2, the mean value per trial was used as a reference (Baseline Measurement). Post-hoc paired-samples t-test with Bonferroni correction were applied to correct for multiple comparison ($p < 0.017$). To evaluate the persistence of any after-effect, the effects of 'Condition' (PS-condition, PC-condition, Baseline Measurement) and 'Time' (Trial 2-5) on LPD, spatiotemporal parameters, and kinematics were determined using a two-way repeated measures analysis of variance. The correlation between the interaction forces measured during the last 40 strides of walking in each condition in LOPES II, and the change in overground LPD from baseline to the post-measurement was calculated using a Pearson's correlation coefficient. In addition, the correlation between the change in LPD from baseline to walking in the robot during the PS- and PC-condition, and the presence of after-effects was calculated using a Pearson's correlation coefficient. The significance level was set at $p < 0.05$ for all tests, unless mentioned otherwise.

Results

Of the 14 healthy adults included, 13 participants completed all assessments (men/women 2/11, age 22.8 ± 2.1 years; length 1.78 ± 0.06 m, weight 71.42 ± 8.63 kg; mean ± SD). One participant was excluded from the analysis, because the PC-condition was not completed due to technical problems.

Table 1. Mean (±SD) values for lateral pelvic displacement (LPD), spatiotemporal gait parameters, and range of motion of the hip and knee joint in the sagittal plane during walking in the robotic gait trainer LOPES II averaged across participants and across strides within the pelvic support (PS) and pelvic constraint (PC) conditions.

	PS	PC
LPD (mm)	105.6 (0.5)	10.8 (0.7) *
Gait velocity (m/s)	0.55 (0.01)	0.55 (0.01)
Cadence (steps/min)	62.8 (3.8)	64.8 (3.2)
Stride length (m)	1.11 (0.09)	1.04 (0.05) *
Stance time (% gait cycle)	58.91 (1.44)	56.77 (0.68) *
Step width (m)	0.16 (0.01)	0.15 (0.01) *
Range of motion		
Hip (degrees)	34.9 (0.9)	34.4 (0.1)
Knee (degrees)	55.0 (0.7)	51.3 (0.2) *

* significantly different from PS ($p < 0.001$).

Lateral pelvic displacement

During robot-assisted gait with pelvic support, the LPD reached an average displacement of 105.6 ± 0.5 mm, which was significantly greater than the LPD during the PC-condition (10.8 ± 0.7 mm; $t(12) = 115.28$, $p < 0.001$; see Table 1). The RMS of the interaction forces during walking in LOPES II was significantly smaller during the PS-condition (RMS: 35.2 ± 11.0 N) compared to the PC-condition (RMS: 73.8 ± 14.7 N; $t(12) = 6.821$, $p < 0.001$).

LPD values recorded during the overground gait analyses are shown in Table 2. In trial 1, the LPD was significantly different between conditions ($F(2,12) = 5.350$, $p = 0.039$). Post-hoc analyses showed that LPD in trial 1 was significantly smaller after the PC-condition compared to the PS-condition ($t(12) = 3.059$, $p = 0.009$; see Figure 4). Compared to baseline, trial 1 after the PC-condition resulted in slightly smaller LPD values and after the PS-condition in slightly larger LPD values, but these differences did not reach significance ($t(12) \leq 1.901$, $p \geq 0.082$). In addition, no main or interaction effects of Condition or Time were found for trials 2-5 ($F(6,132) \leq 0.420$, $p \geq 0.525$). There was no correlation between the individual interaction forces during walking in LOPES II and the presence of after-effects in LPD in either condition (PS: $r = 0.246$, $p = 0.418$; PC: $r = 0.120$, $p = 0.697$; see Figure 5). In addition, there was no correlation between the difference in LPD during walking in the robot and overground walking at baseline, and the presence of after-effects following the PS- ($r = 0.41$, $p = 0.159$) or PC-condition ($r = 0.28$, $p = 0.348$).

Table 2. Mean (±SD) values for lateral pelvic displacement (LPD), spatiotemporal gait parameters, and kinematics during overground walking averaged across participants and across steps within the trial for the baseline (BM) and pelvic support (PS) and pelvic constraint (PC) conditions.

	Trial 1			Trial 2		Trial 3		Trial 4		Trial 5	
	BM	PS	PC	PS	PC	PS	PC	PS	PC	PS	PC
LPD (mm)	36.1 (10.2)	40.1 (9.8)	32.3 *a (12.0)	37.9 (13.9)	37.9 (12.6)	39.1 (15.1)	37.9 (11.8)	39.9 (13.1)	39.5 (12.2)	39.1 (16.9)	37.8 (11.8)
Gait velocity (m/s)	1.36 (0.14)	1.30 (0.17)	1.32 (0.16)	1.34 (0.19)	1.14 (0.45)	1.33 (0.18)	1.35 (0.16)	1.33 (0.19)	1.33 (0.16)	1.32 (0.16)	1.36 (0.16)
Cadence (steps/min)	107.5 (5.0)	104.8 (7.9)	106.5 (5.7)	105.2 (7.1)	105.4 (4.7)	106.4 (6.9)	107.4 (5.1)	104.4 (6.3)	106.2 (5.2)	106.2 (6.8)	107.7 (4.4)
Stride length (m)	1.50 (0.14)	1.49 (0.13)	1.48 (0.14)	1.50 (0.14)	1.46 (0.15)	1.50 (0.14)	1.49 (0.13)	1.51 (0.15)	1.49 (0.15)	1.49 (0.13)	1.49 (0.14)
Stance time (% gait cycle)	62.74 (2.15)	63.26 (1.30)	62.67 (1.90)	63.22 (1.68)	63.21 (1.31)	62.71 (2.16)	62.23 (2.00)	63.19 (1.52)	62.48 (1.62)	62.44 (1.77)	61.85 (1.79)
Step width (m)	0.19 (0.03)	0.20 (0.04)	0.17 *b (0.04)	0.20 (0.03)	0.17 (0.03)	0.19 (0.03)	0.18 (0.03)	0.19 (0.02)	0.19 (0.04)	0.19 (0.02)	0.19 (0.04)
Range of motion											
Hip (degrees)	50.0 (3.6)	50.4 (4.9)	49.4 (3.6)	49.6 (4.4)	49.4 (6.2)	52.0 (6.1)	51.4 (5.3)	49.8 (4.8)	49.2 (4.1)	51.9 (6.0)	53.3 (3.8)
Knee (degrees)	63.8 (2.4)	62.6 (3.4)	62.9 (2.4)	62.3 (4.0)	63.0 (2.9)	62.8 (4.7)	63.0 (4.6)	62.6 (3.2)	62.6 (2.3)	63.2 (3.6)	63.6 (4.8)

*a significantly different from PS in trial 1 ($p=0.009$); *b significantly different from PS and BM in trial 1 ($p=0.013$ and $p=0.013$ respectively).

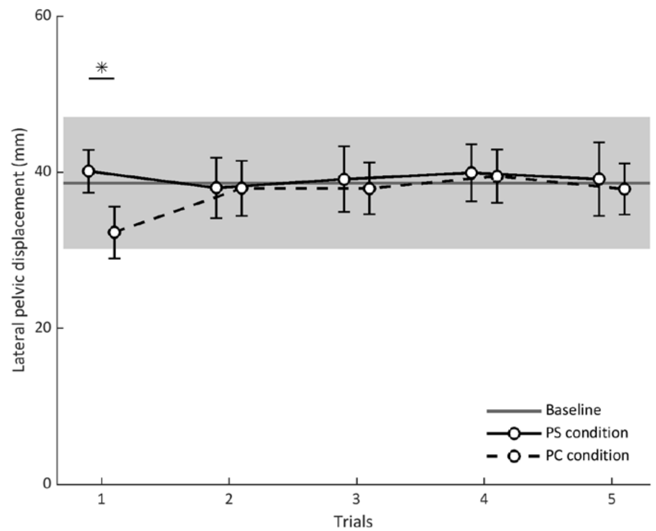

Figure 4. Average lateral pelvic displacement (LPD) recorded during overground walking (trials 1-5) for both baseline measurements, the pelvic support (PS) and pelvic constraint (PC) conditions (N=13). The 95% confidence interval of the baseline LPD across trials is represented by the grey area. Markers represent the LPD values recorded after the PS- (solid line) and PC-conditions (dashed line). Error bars indicate the standard error of the mean.

Spatiotemporal parameters and kinematics

During robot-assisted gait with pelvic constraint, the step length, stance time and step width were significantly smaller than during the PS-condition ($t(12) = 2.229$, $p < 0.05$; $t(12) = 5.449$, $p < 0.001$; and $t(12) = 6.499$, $p < 0.001$ respectively). Knee range of motion was slightly smaller during walking in LOPES II in the PC-condition than in the PS-condition ($t(12) = 4.550$, $p < 0.001$; see Table 1).

Average values for the overground spatiotemporal gait parameters recorded during the baseline measurements and after the PS- and PC-conditions are reported in Table 2. In trial 1, the step width was significantly different between conditions ($F(2,12) = 6.340$, $p = 0.027$). In line with the smaller LPD following the PC-condition, the post-hoc analysis showed that step width was significantly smaller after the PC-condition compared to the PS-condition ($t(12) = 2.925$, $p = 0.013$) and baseline ($t(12) = 2.897$, $p = 0.013$). No main or interaction effects of Condition or Time were found for step width for trial 2-5, or for gait velocity, cadence, stride length, or stance time for any trials. No main or interaction effects of Condition or Time were observed for hip or knee range of motion during trial 1 and trial 2-5 of overground walking.

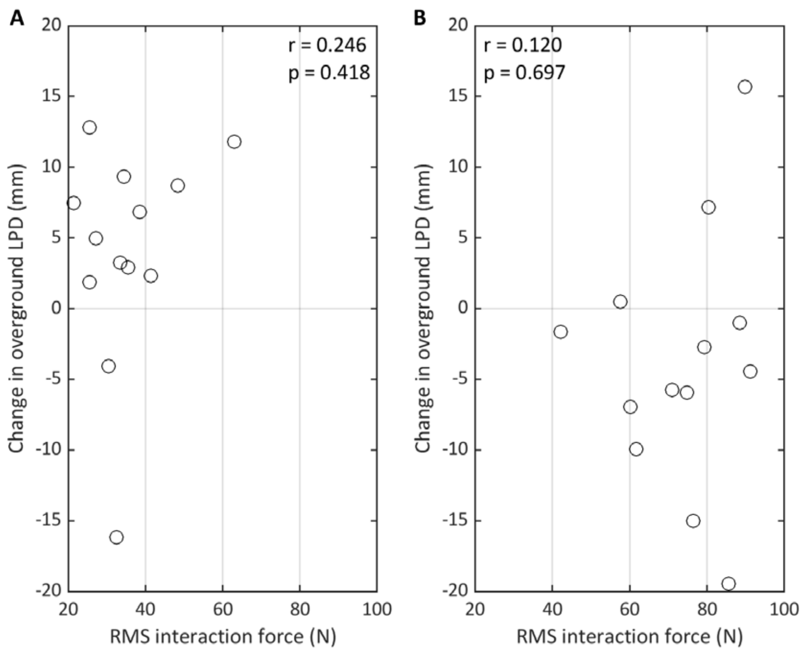

Figure 5. Root mean square (RMS) of the interaction force experienced by each participant during walking in LOPES II in A) the pelvic support and B) pelvic constraint condition plotted against the change from baseline in lateral pelvic displacement (LPD) during overground walking in the respective condition. Accompanying correlation coefficients and p-values are provided. Larger mean RMS interaction forces indicate less adaptation to the movement pattern imposed by the robot. A positive value for the change in LPD indicates that LPD had increased relative to baseline.

Discussion

The aim of the current study was to investigate the immediate after-effect of robot-assisted gait with pelvic support or pelvic constraint on overground walking in healthy adults. As hypothesized, we found that applying a pelvic constraint (PC) reduced the lateral pelvic displacement during the first steps of overground walking in healthy adults when compared to overground walking immediately after the pelvic support (PS) condition. The after-effect in LPD following the PC- compared to PS-condition lasted no longer than one trial (i.e. five steps), which was followed by comparable LPD values across conditions in trials 2-5. In agreement with the reduced LPD in the first trial, the step width also decreased following the PC-condition. Other spatiotemporal gait parameters or kinematics during overground walking were not altered after robot-assisted gait with either pelvic support or pelvic constraint.

Even though participants were able to change their pelvic movements to the applied trajectory in both conditions, the smaller interaction forces measured during the PS-condition reflected a higher level of adaptation to the robot compared to the PC-condition. In the PS-condition, the interaction forces were only marginally higher than those observed for a 'minimal impedance' walking condition resembling free walking (RMS interaction force: 33.5 N; unpublished observations). This suggests that participants actively moved their pelvis along with the pattern imposed by LOPES II, instead of being passively guided by (i.e. pushed) or working against the robot. In the PC-condition, the larger interaction forces raise the question as to whether the participants (partly) reduced their active pelvic movements to the imposed constraint; or whether they were trying hard to move their pelvis and actively worked against the robotic constraint. The answer to this question can only be speculated upon from the direction of the observed after-effects. Previous adaptation studies in which participants had to adapt to a perturbing force while performing a movement, involved generating opposing forces and joint torques to perform the movement correctly. In these experiments, an overshoot of the movement was typically observed after removal of the perturbation[15-17]. Hence, the LPD 'undershoot' following the PC-condition in the present study suggests that our participants did not actively work against the robotic constraint, but indeed (partly) adapted to the robotic constraint.

The finding that walking in the robotic gait trainer with constrained lateral translation and rotation of the pelvis tends to affect the *subsequent* overground gait pattern in healthy adults adds to previous studies reporting altered gait *during* walking with a pelvic constraint[9,10] and following walking with a constraint of the lower extremity on a treadmill1[5-17] or pelvis[12,18]. In agreement with our findings, these studies showed decreased range of motion at the knee and hip joints[10] and smaller step widths[9,12] during walking with constrained lateral translations and rotations of the pelvis. In the present study, we also demonstrate a significant after-effect on overground LPD and step width following walking in a robotic gait trainer with a pelvic constraint. The reduced LPD during overground walking following the PC-condition is in line with previous studies conducted on a treadmill. These studies showed that constrained or supported pelvic translations resulted in reduced or enlarged pelvic movements and step width during unconstrained treadmill walking, respectively[12,19]. The smaller step width observed in our study during overground walking might be due to the applied pelvic constraint in combination with the decreased step width *during* walking in the robotic gait trainer.

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Although present, the observed after-effect on LPD and step width of walking with pelvic constraint in the present study was relatively small and quickly disappeared over time. The relative duration and size of the observed after-effect was modest compared to previous results from locomotor adaptation studies in healthy subjects. A review by Reisman et al[20] reported after-effects ranging from 20 strides to 30 minutes following 5-180 minutes of walking in an experimental condition. This discrepancy may be due to the varying duration and type of applied conditions. For example, short after-effects (13-20 steps) were observed after 188 steps of walking in a robotic gait trainer with resistance applied to the hip and knee[21], whereas 10 minutes of split-belt training induced more persistent after-effects, lasting up to 6 minutes[22]. Based on the duration of the currently applied pelvic condition, a longer after-effect might have been expected. However, as after-effects are supposed to be greatest when the training and experimental conditions are similar[23-25], the transition from the robotic gait trainer to overground walking at a higher velocity might have reduced the observed after-effect. The difference in velocity between walking overground and in the LOPES II may be considered a limitation of the study.

Another limitation of the current study is the difference between the PC- and PS-condition in the general guidance force applied to the lower limbs. Yet, we purposely chose to apply the maximum general guidance force during the PC-condition, as these settings closely resemble the procedures used by first-generation robotic gait trainers[26]. On the other hand, newer robotic gait trainers can support the pelvic movements and also allow adjusting the guidance levels to the individual patient's needs[14]. As we aimed to resemble the training conditions in older versus newer robotic gait trainers, we selected lower levels of general guidance force during the PS-condition. Because of this deliberate difference between the PS- and PC-conditions, we cannot rule out the possibility that the greater general guidance force in the PC-condition may have influenced (i.e. increased or decreased) the observed after-effects in LPD and step width during overground walking.

The reduced LPD and accompanying decrease in step width during overground walking in healthy controls following the pelvic constraint condition may have implications for robot-assisted gait training in people with neurological disorders (e.g. stroke, spinal cord injury). First-generation robotic gait trainers used for rehabilitation have limited control over the pelvic movements and constrain the pelvis during walking[11]. The present results indicate that these pelvic restrictions have the potential to undesirably carry over to overground walking. This effect was very short-lived in our healthy young participants after only 20-minutes of walking with pelvic constraint, yet repeated exposure and adaptation to a perturbation may result in longer lasting or even permanent changes in motor behavior[27]. Results from classical perturbation studies show that individuals with neurological disorders adapt differently to the applied perturbation compared to healthy controls. These individuals seem to be less capable to adapt[28], need more time to adapt[29], and their adaptation may vary greatly between individuals[30]. As pelvic constraint interferes with frontal plane balance control, we expect that constrained pelvic movements have a negative impact on the overground walking pattern of individuals with impaired gait due to a neurological disorder. In particular, individuals suffering from severe balance problems in the frontal plane and individuals with an ataxic gait pattern may experience such a negative impact of pelvic constraint on overground walking. It remains for future research to identify if individuals with impaired gait due to neurological disorders adapt to applied pelvic constraints during robotic gait training, and whether this may have a negative impact on the overground walking pattern. And if so, whether pelvic support during robot-assisted gait training may be superior to a pelvic constraint for promoting gait recovery in individuals with neurological disorders.

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Conclusions

This cross-over study shows that robot-assisted gait training with pelvic constraint has an immediate negative after-effect on the overground walking pattern in healthy subjects as compared to robot-assisted gait training with pelvic support. The after-effects were relatively small and short-lived, yet the effect of applying pelvic constraint or support during robot-assisted gait training in people with neurological gait impairments remains to be determined.

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References

1. Bohannon RW, Andrews AW, Smith MB. Rehabilitation goals of patients with hemiplegia. Int J Rehabil Res. 1988;11(2):181-184.
2. Patterson KK, Parafianowicz I, Danells CJ, et al. Gait asymmetry in community-ambulating stroke survivors. Arch Phys Med Rehabil. 2008;89(2):304-310.
3. Chen G, Patten C, Kothari DH, Zajac FE. Gait differences between individuals with post-stroke hemiparesis and non-disabled controls at matched speeds. Gait Posture. 2005;22(1):51-56.
4. Dodd KJ, Morris ME. Lateral pelvic displacement during gait: abnormalities after stroke and changes during the first month of rehabilitation. Arch Phys Med Rehabil. 2003;84(8):1200-1205.
5. Saunders JB, Inman VT, Eberhart HD. The major determinants in normal and pathological gait. J Bone Joint Surg Am. 1953;35(3):543-558.
6. Schwartz I, Sajin A, Fisher I, et al. The effectiveness of locomotor therapy using robotic-assisted gait training in subacute stroke patients: a randomized controlled trial. PM & R. 2009;1(6):516-523.
7. Nam KY, Kim HJ, Kwon BS, Park JW, Lee HJ, Yoo A. Robot-assisted gait training (Lokomat) improves walking function and activity in people with spinal cord injury: a systematic review. J Neuroeng Rehabil. 2017;14(1):24.
8. Wallard L, Dietrich G, Kerlirzin Y, Bredin J. Effect of robotic-assisted gait rehabilitation on dynamic equilibrium control in the gait of children with cerebral palsy. Gait Posture. 2018;60:55-60.
9. Veneman JF, Menger J, Van Asseldonk EH, Van der Helm FC, Van der Kooij H. Fixating the pelvis in the horizontal plane affects gait characteristics. Gait Posture. 2008;28(1):157-163.
10. Mun KR, Guo Z, Yu H. Restriction of pelvic lateral and rotational motions alters lower limb kinematics and muscle activation pattern during over-ground walking. Med Biol Eng Comput. 2016;54(11):1621-1629.
11. Hidler JM, Wall AE. Alterations in muscle activation patterns during robotic-assisted walking. Clin Biomech. 2005;20(2):184-193.
12. Kang J, Vashista V, Agrawal SK. On the Adaptation of Pelvic Motion by Applying 3-dimensional Guidance Forces Using TPAD. IEEE Trans Neural Syst Rehabil Eng. 2017;25(9):1558-1567.
13. Veneman JF, Kruidhof R, Hekman EE, Ekkelenkamp R, Van Asseldonk EH, Van der Kooij H. Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):379-386.
14. Meuleman J, Van Asseldonk E, Van Oort G, Rietman H, Van der Kooij H. LOPES II--Design and Evaluation of an Admittance Controlled Gait Training Robot With Shadow-Leg Approach. IEEE Trans Neural Syst Rehabil Eng. 2016;24(3):352-363.
15. Cajigas I, Goldsmith MT, Duschau-Wicke A, et al. Assessment of lower extremity motor adaptation via an extension of the force field adaptation paradigm. Annu Int Conf IEEE Eng Med Biol Soc. 2010;2010:4522-4525.
16. Noble JW, Prentice SD. Adaptation to unilateral change in lower limb mechanical properties during human walking. Exp Brain Res. 2006;169(4):482-495.
17. Savin DN, Tseng SC, Morton SM. Bilateral adaptation during locomotion following a unilaterally applied resistance to swing in nondisabled adults. J Neurophysiol. 2010;104(6):3600-3611.
18. Vashista V, Agrawal N, Shaharudin S, Reisman DS, Agrawal SK. Force adaptation in human walking with symmetrically applied downward forces on the pelvis. IEEE Trans Neural Syst Rehabil Eng. 2013;21(6):969-978.
19. Kang J, Vashista V, Agrawal SK. A novel assist-as-needed control method to guide pelvic trajectory for gait rehabilitation. IEEE ICORR. 2015;2015:630-635.
20. Reisman DS, Bastian AJ, Morton SM. Neurophysiologic and rehabilitation insights from the split-belt and other locomotor adaptation paradigms. Phys Ther. 2010;90(2):187-195.
21. Lam T, Anderschitz M, Dietz V. Contribution of feedback and feedforward strategies to locomotor adaptations. J Neurophysiol. 2006;95(2):766-773.
22. Reisman DS, Block HJ, Bastian AJ. Interlimb coordination during locomotion: what can be adapted and stored? J Neurophysiol. 2005;94(4):2403-2415.
23. Reisman DS, Wityk R, Silver K, Bastian AJ. Split-belt treadmill adaptation transfers to overground walking in persons poststroke. Neurorehabil Neural Repair. 2009;23(7):735-744.
24. Torres-Oviedo G, Bastian AJ. Seeing is believing: effects of visual contextual cues on learning and transfer of locomotor adaptation. J Neurosci. 2010;30(50):17015-17022.
25. Torres-Oviedo G, Bastian AJ. Natural error patterns enable transfer of motor learning to novel contexts. J Neurophysiol. 2012;107(1):346-356.
26. Colombo G, Joerg M, Schreier R, Dietz V. Treadmill training of paraplegic patients using a robotic orthosis. J Rehabil Res Dev. 2000;37(6):693-700.
27. Schmidt RA. Motor control and learning: a behavioral emphasis. 2nd ed. Champaign, IL: Human Kinetics Publishers; 1988.
28. Takahashi CD, Reinkensmeyer DJ. Hemiparetic stroke impairs anticipatory control of arm movement. Exp Brain Res. 2003;149(2):131-140.
29. Malone LA, Bastian AJ. Spatial and temporal asymmetries in gait predict split-belt adaptation behavior in stroke. Neurorehabil Neural Repair. 2014;28(3):230-240.
30. Morton SM, Bastian AJ. Cerebellar contributions to locomotor adaptations during splitbelt treadmill walking. J Neurosci. 2006;26(36):9107-9116.

2

Chapter 3

Effect of assist-as-needed robotic gait training on the gait pattern post stroke: a randomized controlled trial

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Abstract

Background

Regaining gait capacity is an important rehabilitation goal post stroke. Compared to clinically available robotic gait trainers, robots with an assist-as-needed approach and multiple degrees of freedom (AAN_{mDOF}) are expected to support motor learning, and might improve the post-stroke gait pattern. However, their benefits compared to conventional gait training have not yet been shown in a randomized controlled trial (RCT). The aim of this two-center, assessor-blinded, RCT was to compare the effect of AAN_{mDOF} robotic to conventional training on the gait pattern and functional gait tasks during post-stroke inpatient rehabilitation.

Methods

Thirty-four participants with unilateral, supratentorial stroke were enrolled (<10 weeks post onset, Functional Ambulation Categories 3-5) and randomly assigned to six weeks of AAN_{mDOF} robotic (combination of training in LOPES II and conventional gait training) or conventional gait training (30 minutes, 3-5 times a week), focused on pre-defined training goals. Randomization and allocation to training group were carried out by an independent researcher. External mechanical work (W_{EXT}), spatiotemporal gait parameters, gait kinematics related to pre-defined training goals, and functional gait tasks were assessed before training (T0), after training (T1), and at 4-months follow-up (T2).

Results

Two participants, one in each group, were excluded from analysis because of discontinued participation after T0, leaving 32 participants (AAN_{mDOF} robotic n=17; conventional n=15) for intention-to-treat analysis. In both groups, W_{EXT} had decreased at T1 and had become similar to baseline at T2, while gait speed had increased at both assessments. In both groups, most spatiotemporal gait parameters and functional gait tasks had improved at T1 and T2. Except for step width (T0-T1) and paretic step length (T0-T2), there were no significant group differences at T1 or T2 compared to T0. In participants with a pre-defined goal aimed at foot clearance, paretic knee flexion improved more in the AAN_{mDOF} robotic group compared to the conventional group (T0-T2).

Conclusions

Generally, AAN_{mDOF} robotic training was not superior to conventional training for improving gait pattern in subacute stroke survivors. Both groups improved their mechanical gait efficiency. Yet, AAN_{mDOF} robotic training might be more effective to improve specific post-stroke gait abnormalities such as reduced knee flexion during swing.

Trial registration: Netherlands Trial Register (www.trialregister.nl): NTR5060. Registered 13 February 2015.

Introduction

Regaining gait capacity is one of the most reported rehabilitation goals post stroke[1-3]. Besides basic gait independence and the ability to adapt gait to environmental demands, rehabilitation is often focused on optimizing the individual gait pattern, particularly in the early phase post stroke. After unilateral supratentorial stroke, the hemiparetic gait pattern is commonly characterized by pes equinovarus during swing and/or loading[4], knee instability during early and/or midstance[5,6], impaired ankle plantarflexion power during push-off[4], and reduced knee flexion during (pre)swing of the paretic leg[5]. As a consequence, asymmetry in step length[5] and/or single support time are observed in many patients with post-stroke hemiparesis[7]. In addition, hemiparetic gait is associated with reduced gait speed[8], increased fall risk[9], and limited community ambulation[10]. Hence, improving the post-stroke gait pattern is an important rehabilitation goal.

Robotic gait training has the potential to improve the post-stroke gait pattern[11-17], but its benefits compared to conventional gait training are still under debate[11-18]. Most clinically available robotic gait trainers lack the ability to adjust the robotic actuation based on the user's performance, which may restrain motor learning[18]. In contrast, robotic gait trainers with a so called 'assist-as-needed' (AAN) approach adapt guidance to the user's needs[19,20] and allow support of specific subtasks of the gait cycle[20], thereby promoting active involvement of the user and, thus, motor learning[21-23]. Furthermore, robotic gait trainers with ample degrees of freedom allow a (near) normal gait pattern, in particular with respect to active balance control during walking[21,24]. In addition, sufficient allowance of movement variability optimizes the amount of error information needed for motor learning[25]. Consequently, robotic gait training with AAN principles and multiple degrees of freedom (AAN_{mDOF}) has the potential to improve gait post stroke. However, no evidence from randomized controlled trials is yet available for its superiority compared to conventional gait training, in particular with regard to the gait pattern, during primary inpatient stroke rehabilitation.

As nearly all kinematic gait deviations and/or spatiotemporal gait abnormalities are translated into irregular movements of the body center of mass of the body (COM), we evaluated the quality of the post-stroke gait pattern based on the COM trajectory. COM movement relative to its surroundings is represented by external mechanical work (W_{EXT})[26]. In healthy individuals who walk at their preferred speed, COM movements in directions other than the walking direction are typically minimized[27], and W_{EXT} is relatively small. Stroke survivors, however, often show compensatory movements in the frontal, sagittal and/or transversal planes while walking, resulting in irregular and enlarged COM trajectories[28] and increased W_{EXT}[29], reflecting a reduced quality of the gait pattern. As increased gait speed is generally associated with increased W_{EXT}[30,31], interpretation of changes in W_{EXT} should be related to changes in gait speed.

The primary aim of the present study was to evaluate whether six weeks AAN_{mDOF} robotic gait training would be superior to conventional gait training in terms of W_{EXT} in stroke survivors during their inpatient rehabilitation. A secondary aim was to evaluate whether this effect would be retained four months after the intervention. We hypothesized that, given a similar increase in gait speed between groups, the increase in W_{EXT} would be smaller following robotic training compared to conventional training one week and four months after the intervention period. A third aim was to evaluate the AAN_{mDOF} robotic gait training on spatiotemporal gait parameters, kinematics related to pre-defined training goals, and functional gait tasks.

Methods

Participants

Stroke survivors admitted for inpatient rehabilitation to two rehabilitation centers in the Netherlands (Sint Maartenskliniek, Nijmegen; Roessingh Center for Rehabilitation, Enschede) were assessed for eligibility by their treating rehabilitation physician or physical therapist from October 2015 until June 2019. Inclusion criteria were: 1) adult (≥ 18 years of age) after a first or recurrent unilateral ischemic or hemorrhagic supratentorial stroke (< 10 weeks post onset), 2) impairment of one or more prerequisites of gait according to Gage et al[32]. Exclusion criteria were: 1) inability to walk without support, with or without supervision (Functional Ambulation Category (FAC) 0-2), 2) medical conditions interfering with gait, 3) inability to understand verbal instructions, 4) severe visual problems e.g. hemianopia or visuospatial neglect, 5) no independent ambulation prior to stroke, 6) depressed mood assessed with the Hospital Anxiety and Depression Scale (HADS > 7), 7) severe lower limb spasticity (at any level) assessed with the Modified Ashworth Scale (MAS ≥ 3), 8) severe lower limb contracture (at any level) determined by a physical examination, 9) body weight ≥ 140 kg, 10) skin problems at any body site where the support harness or straps of the robotic gait trainer were to be fitted, and 11) expected length of stay in rehabilitation center < 6 weeks. Exclusion criteria 7 to 10 were applied primarily to prevent inappropriate or unsafe fitting of the robotic gait trainer. Individuals who were eligible and willing to participate received study information from the researcher. All participants gave written informed consent before definitive inclusion, in accordance with the Declaration of Helsinki. Demographic and clinical characteristics were collected: sex (male/female), height (cm), hemiparetic side (left/right), use of ankle-foot orthosis (yes/no), lower limb motor impairment (Fugl Meyer Assessment[33] – leg score; 0-34), lower limb strength (Motricity Index[34] – leg score; 0-100), cognition (Montreal Cognitive Assessment[35] (MoCA); 0-30), and communication skills (Utrechts Communicatie Onderzoek[36] (UCO) – subscale conversation; 1-5).

Study design and randomization

This study was conducted as a two-center, assessor-blinded, randomized controlled, parallel group trial. The study protocol (NL 50748.044.14) was approved by the Medical Ethical Committee Twente (Enschede, the Netherlands) and registered in the Netherlands Trial Register (NTR5060). Figure 1 provides an overview of the study design. Assessments were performed before (T0), within one week after (T1), and four months after (T2) the six-week intervention period. At each center, all assessments were performed by one assessor who was blinded for group allocation. After completing the T0 assessment, a stratified block randomization with an allocation ratio of 1:1 was used. Participants were stratified by baseline gait speed (≤ 0.4 m/s or > 0.4 m/s) and allocated to the AAN_{mDOF} robotic or conventional gait training groups using random permuted blocks (block sizes two and four) within each strata. An independent researcher generated the random allocation sequence, transferred it to numbered envelopes, and handed the envelope to the participant to inform about the group allocation after completing the T0 assessment.

Intervention

Prior to the start of the training an individual training goal was selected by a rehabilitation physician based on clinical examination. The pre-defined training goals were derived from the kinematic aspects of the prerequisites of gait defined by Gage et al[32] and were operationalized as improving: foot clearance (swing), knee stability (stance), limb loading (stance), or foot prepositioning (swing). The AAN_{mDOF} robotic gait training group received three 30-minute sessions of individually tailored LOPES II training per week. LOPES II is a treadmill-based AAN_{mDOF} robotic gait trainer, combined with a body-weight support system (MOOG BV, Nieuw-Vennep, the Netherlands). LOPES II has eight powered degrees of freedom, actuating pelvic translations in the anterior/posterior and lateral directions, hip flexion/extension, hip adduction/abduction, and knee flexion/extension. Ankle dorsiflexion movements can be supported using toe-lifters or conventional ankle-foot orthoses. For a detailed description of the LOPES II see Meuleman et al[20]. At the start of the training, individually-tailored, minimal levels of body-weight support and general and specific guidance forces were determined at which the participant was just able to match the reference gait trajectories, related to the pre-defined training goal, of the LOPES II. Across the training sessions, the goal was to match the reference gait trajectories of the LOPES II, while gradually reducing the level of body-weight support, reducing the general and specific guidance forces, and increasing the gait speed. Real-time feedback about the participant's gait pattern was provided by the user interface of LOPES II, complemented by verbal feedback from the treating physical therapist. AAN_{mDOF} robotic gait training was complemented with a maximum of two 30-minute individual gait training sessions per week, according to the latest insights in neurorehabilitation[37]. Thus, when using the term AAN_{mDOF} robotic gait training in the remainder of this text, this refers to a combination of robotic gait training in LOPES II and conventional therapy. The training frequency and LOPES II settings were documented in a logbook.

The conventional training group received three to five 30-minute individual gait training sessions per week, according to the latest insights in neurorehabilitation[37]. Physical therapists provided verbal feedback about the participant's performance with emphasis on attainment of the individual primary training goal. The training frequency was documented in a logbook. Both the AAN_{mDOF} robotic and conventional gait training group could receive group training as part of their regular gait rehabilitation program, in addition to the scheduled individual gait training sessions per week. The training frequency of the group sessions was documented in a logbook. Use of interactive treadmill or other robotic gait trainers was not allowed during the intervention period. After the end of the intervention period (after the T1 assessment), participants were allowed to continue their regular (inpatient or outpatient) rehabilitation program, but these gait training sessions were no longer logged.

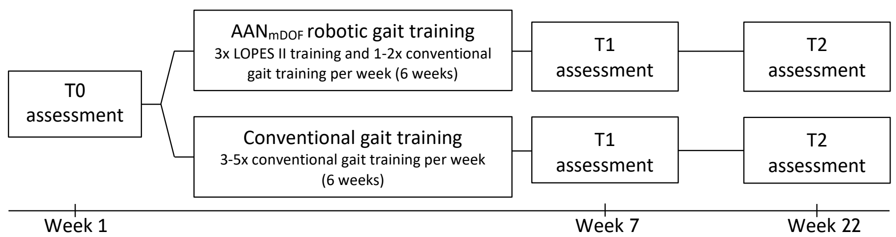

Figure 1. Study design

Procedure

During each assessment a 3D-gait analysis was performed. Reflective markers (n=39) were attached to the participant according to the Plug-In-Gait Full Body model (Plug-In-Gait, Vicon Motion Systems Ltd, Oxford, UK). Marker positions were recorded by infrared cameras (f_S = 100 Hz; Vicon mX 1.7.1, Oxford Metrics, UK). Participants were instructed to walk at their self-selected speed along a straight 6-meter walkway. Participants wore their own shoes and were allowed to use an ankle-foot orthosis if necessary, which could vary between assessments as a consequence of motor recovery. Use of other walking aids was not allowed. At least 15 strides were collected during each assessment. Data was analyzed using custom written software (MATLAB, Mathworks Inc, Natick, MA, USA). Initial contact and foot-off were determined with the velocity-based algorithm as described by Zeni et al[38].

Outcomes

Primary outcome measure

The primary outcome W_{EXT} was determined per stride through analysis of the energy changes at the level of the COM relative to the surroundings[26]. The energy level of the body (E_{EXT}) is determined by the sum of potential and kinetic energy of the COM per stride:

$$E_{EXT} = \frac{1}{2}MV_{forward}{}^2 + \left(MgH + \frac{1}{2}MV_{vertical}{}^2\right) + \frac{1}{2}MV_{lateral}{}^2$$

where M is the total body mass (kg), g is gravity (m/s²), and H and V are the height (m) and velocity in the forward, vertical and lateral direction (m/s) of the COM relative to the surrounding. W_{EXT} is defined as the sum of the increments of the E_{EXT} curve per stride. W_{EXT} was normalized for body mass and stride length (J/kg/m). As W_{EXT} is associated with walking velocity[30,31], W_{EXT} is always reported together with gait speed.

Secondary outcome measures

The following spatiotemporal parameters were calculated using the marker data collected from each trial of the 3D-gait analysis: gait speed (m/s), step width (m), step length (m), and single-support time (% gait cycle). Symmetry ratios were calculated for step length and single-support time, and expressed as the absolute difference from 0.5 (perfect symmetry), according to the following equation:

$$Symmetry\ ratio = \left|\, 0.5 - \frac{Parameter_{paretic\ leg}}{Parameter_{non-paretic\ leg} + Parameter_{paretic\ leg}} \,\right|$$

In addition, the following functional gait tasks and clinical leg motor scores were recorded during each assessment: 6-Minute Walk Test[39], 10-Meter Walk Test[40], Timed Up and Go Test[41], Functional Gait Assessment[42], Fugl Meyer Assessment[33] – leg score, and Motricity Index[34] – leg score. Participants were allowed to use an ankle-foot orthosis and/or a walking aid during the functional gait tasks when necessary.

Individual training goals

To evaluate the training effects on the pre-defined training goals, Vicon Plug-In-Gait model and software were used to calculate the individual gait kinematics per stride. Foot clearance, knee stability in stance (reduction in knee extension thrust), limb loading and foot prepositioning were evaluated by maximal knee flexion of the paretic leg during early swing, the difference in maximal knee extension velocity between the paretic and non-paretic leg during single-support phase, single-support time symmetry, and minimal knee flexion of the paretic leg during terminal swing, respectively.

Power calculation

Power analysis performed using STATA version 10.1 showed that a sample size of 50 participants (α = 0.05, β = 0.10, including 10% drop-out) was sufficient to demonstrate a group difference in W_{EXT} of 0.13 J/kg/m after the intervention[43].

Statistical analysis

All statistical analyses were performed using SPSS statistics version 19 (IBM SPSS Statistics, Chicago, USA). Baseline characteristics were compared between groups using independent t-tests or Mann-Whitney U tests for continuous variables, and chi-square tests for categorical variables. W_{EXT}, spatiotemporal parameters, and gait kinematics were averaged per individual over all strides per assessment (T0-T2). Effects of the intervention at T1 and T2 on primary and secondary outcomes were separately analyzed, according to an 'intention-to-treat' principle, using linear mixed model for repeated measures with a fixed effect for Group (AAN_{mDOF} robotic vs conventional) and Time (T0 vs T1, or T0 vs T2). All linear mixed models used a restricted maximum likelihood estimation to obtain the results, an unstructured covariance matrix, and Šidák adjustment for multiple testing. Effects of the intervention on the pre-defined training goals were analyzed per subgroup of participants with the same pre-defined training goal (n≥10), according to an 'per-protocol' analysis, using non-parametric Mann-Whitney U tests on difference scores for each outcome (T0 vs T1, or T0 vs T2). The significance level was set at $p < 0.05$ for all tests.

Results

The participants' flow is presented in Figure 2. Recruitment started in October 2015 and was stopped in June 2019 due to end of funding. Thirty-four individuals were randomly assigned to the AAN_{mDOF} robotic (n = 18; gait speed < 0.4 m/s, n = 7) or conventional gait training group (n = 16; gait speed < 0.4 m/s, n = 6). Two participants, one in each group, discontinued participation directly after T0, because they expected the study protocol to be too physically demanding. Hence 32 participant were included in the intention-to-treat analysis (AAN_{mDOF} robotic n = 17; conventional n = 15). One participant discontinued the robotic gait training, because the study protocol was too physically demanding. Another four subjects (AAN_{mDOF} robotic n = 3; conventional n = 1) were lost to follow-up after the post-intervention assessment, because of time requirements (n = 2) or medical reasons unrelated to the study (n = 2). Baseline demographic and clinical characteristics, and individual training goals did not differ between groups (see Table 1).

Details of interventions and adverse effects

In the robotic training group, one participant discontinued training after 2 sessions, whereas the other participants received a median of 15 (interquartile range (IQR): 13.8 – 15.3) individual robotic gait training sessions. In accordance with the training protocol, a reduction in average body weight support (week 1: 8.3 ± 5.6 %; week 6: 6.7 ± 3.5 %), general guidance force (week 1: 61.1 ± 22.0 %; week 6: 22.2 ± 25.6 %), and specific guidance force (week 1: 42.8 ± 21.8 %; week 6: 25.0 ± 23.2 %) was applied, while average gait speed was increased (week 1: 1.60 ± 0.51 km/h;

week 6: 2.40 ± 0.62 km/h) across the robotic training sessions. In addition to the robotic gait training, participants in this group received a median of 11 (IQR: 7.5 – 12.0) individual and 6 (IQR: 4.8 – 10.5) group sessions of conventional gait training, resulting in a total median number of 32 (IQR: 26.0 – 37.8) training sessions during the intervention period. The conventional training group received a median of 18 (IQR: 14.5 – 22.0) individual and 9 (IQR: 7.5 – 12.0) group sessions of conventional gait training, resulting in a total median number of 27 (IQR: 22.0 – 34.0) training sessions during the intervention period. One participant experienced a fall with wheelchair, outside the study context, but was able to continue conventional gait training after one week of rest. No additional adverse events were reported.

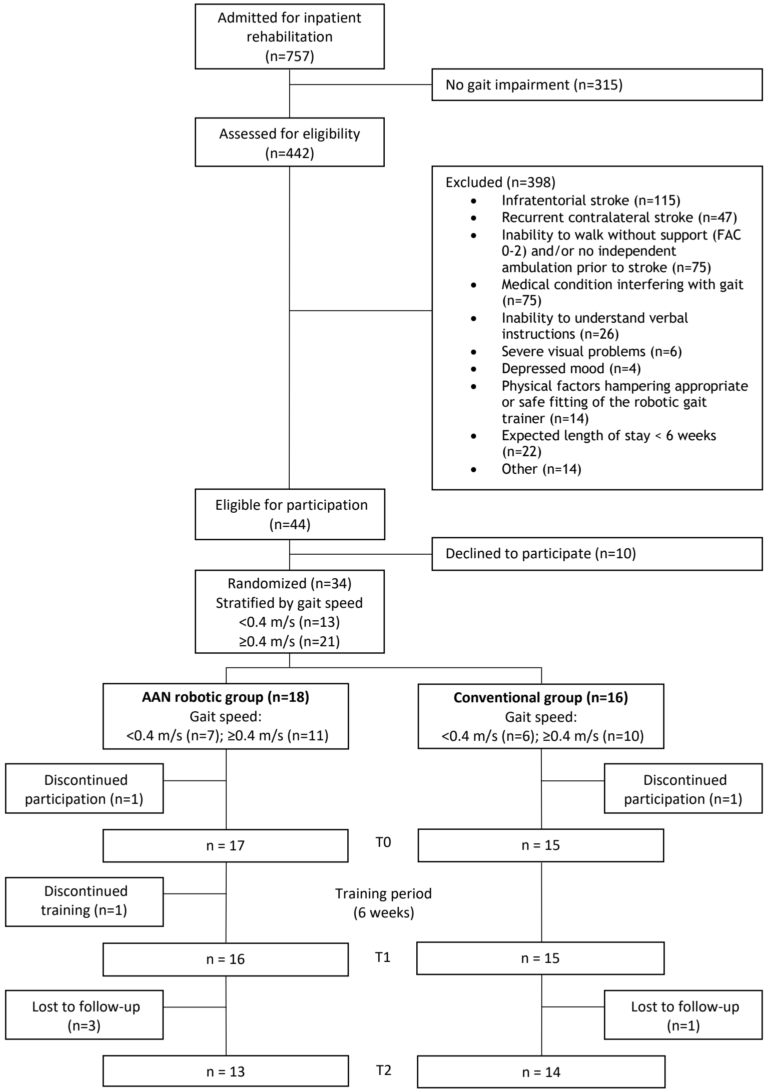

Figure 2. CONSORT Flowchart.

Table 1. Baseline demographic, clinical characteristics, and individual training goals for the AAN_{mDOF} robotic and conventional gait training groups (mean ± SD or number).

	AAN_{mDOF} robotic n=17	Conventional n=15
Sex, male/female (n)	10/7	10/5
Age (years)	60.6 ± 9.3	56.8 ± 9.8
Height (cm)	177.4 ± 7.6	177.7 ± 7.5
Weight (kg)	80.8 ± 16.0	79.3 ± 14.3
Type of stroke, ischemic/haemorrhagic (n)	13/4	11/4
Time since stroke (wks)	5.4 ± 1.8	5.9 ± 2.1
Hemiparetic side, left/right (n)	7/10	7/8
Use of ankle-foot orthosis (n)	8	6
FAC score (n)		
3	10	6
4	6	8
5	1	1
Fugl Meyer Assessment – leg score	24.2 ± 4.6	23.4 ± 6.8
Motricity Index – leg score	63.9 ± 17.0	62.5 ± 26.4
HADS – subscale depression	1.8 ± 1.5	1.2 ± 0.9
MoCA	24.1 ± 4.2	23.4 ± 4.1
UCO - subscale conversation (n)		
4	0	2
5	17	13
Individual training goal (n)		
Foot clearance	6	6
Knee stability	6	7
Limb loading	4	2
Foot prepositioning	1	0

FAC score: Functional Ambulation Category (range 0-5), Fugl Meyer Assessment – leg score (range 0–34), Motricity Index – leg score (range 0–100), HADS: Hospital Anxiety and Depression Scale – subscale depression (range 0–21), MoCA: Montreal Cognitive Assessment (range 0–30), UCO: Utrechts Communicatie Onderzoek – subscale conversation (range 1–5)

External mechanical work and gait speed

Group results of W_{EXT} and gait speed are summarized in Table 2. The corresponding test statistics are reported in Supplementary Table S1. Irrespective of group allocation (*Group x Time* interactions, p ≥ 0.438), W_{EXT} significantly decreased from T0 to T1 (mean difference = -0.09 J/kg/m; 95% CI: -0.17 to -0.01, p = 0.039), while gait speed significantly increased from T0 to T1 (mean difference = 0.15 m/s; 95% CI: 0.08 - 0.22, p < 0.001) (see Figure 3). Figure 4 shows that 21 out of 31 participants who completed both assessments had lower W_{EXT} at T1. Seventeen of them (81%) showed a concurrent increase in gait speed, whereas four participants (19%) showed a concurrent decrease in gait speed. Of the 10 participants with increased W_{EXT} at T1, eight (80%) showed a concurrent increase and two (20%) a decrease in gait speed. Between T0 and T2, W_{EXT} did not significantly differ (p = 0.263), while gait speed significantly increased in the same time period (mean difference = 0.26 m/s; 95% CI: 0.18 - 0.34; $p < 0.001$) (see Figure 3). These *Time* effects did not differ between groups (*Group x Time* interactions, $p \geq 0.152$).

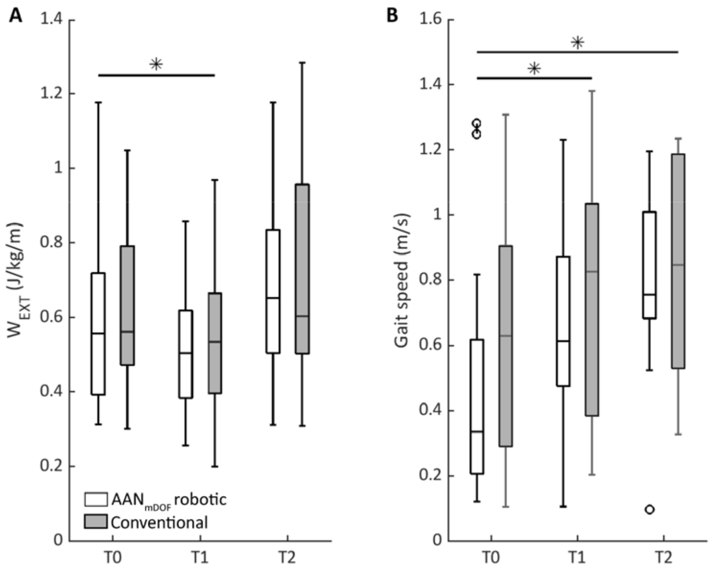

Figure 3. Course of change in A) external mechanical work and B) gait speed across assessments (T0-T2) in the AAN_{mDOF} robotic and conventional gait training groups. Each box represents the median, and upper and lower quartiles of the variable, with whiskers extended to the extreme values. Outliers are represented by markers. * significant *Time* effect ($p < 0.05$)

Secondary outcomes

Paretic and non-paretic step length, paretic single-support time, step length and single-support time symmetry, and all functional gait tasks and clinical scores significantly improved from T0 to T1 (improvements ranging from 7.4 to 37.9%; $p \leq 0.049$) and T0 to T2 (improvements ranging from 14.5% to 67.6%; $p \leq 0.019$) (see Table 2 and Supplementary Table S1). In addition, non-paretic single-support time improved from T0 to T1 ($p = 0.005$), and did not differ between T0 and T2 ($p = 0.075$). Most *Time* effects were similar for both groups from T0 to T1 (*Group x Time* interactions $p \geq 0.106$), as well as from T0 to T2 (*Group x Time* interactions $p \geq 0.063$). From T0 to T1, the only significant difference between group was found for step width, which remained constant following robotic gait training, whereas it increased by 2 cm after conventional training (*Group x Time* interaction $p = 0.018$). Step width was similar for both groups between T0 to T2 (*Group x Time* interaction $p = 0.055$). Furthermore, from T0 to T2, the increase in paretic step length was larger following robotic gait training (16 cm) compared to conventional gait training (6 cm; *Group x Time* interaction $p = 0.027$). There were no main effects of *Group* for any outcome from T0 to T1 ($p \geq 0.152$) or from T0 to T2 ($p \geq 0.201$).

Table 2. Means (± SDs) of mechanical work, spatiotemporal gait parameters, functional gait tasks, and clinical scores for the AAN_{mDOF} robotic and conventional gait training groups, before (T0), immediately after (T1), and four months after (T2) the six-week intervention period.

	AAN_{mDOF} robotic			Conventional		
	T0	T1	T2	T0	T1	T2
	n=17	n=16	n=13	n=15	n=15	n=14
Mechanical work						
W_{EXT} (J/kg/m) *	0.61 ± 0.25	0.52 ± 0.18	0.69 ± 0.26	0.63 ± 0.23	0.53 ± 0.20	0.70 ± 0.29
Spatiotemporal parameters						
Gait speed (m/s) * **	0.47 ± 0.36	0.67 ± 0.29	0.81 ± 0.24	0.62 ± 0.36	0.75 ± 0.38	0.81 ± 0.32
Step width (m) * †	0.15 ± 0.04	0.15 ± 0.05	0.14 ± 0.05	0.16 ± 0.06	0.18 ± 0.06	0.17 ± 0.06
Step length						
Paretic (m) * ** ‡	0.35 ± 0.15	0.46 ± 0.11	0.51 ± 0.10	0.43 ± 0.13	0.48 ± 0.13	0.49 ± 0.12
Non-paretic (m) * **	0.33 ± 0.17	0.44 ± 0.14	0.50 ± 0.09	0.39 ± 0.20	0.46 ± 0.19	0.50 ± 0.15
Symmetry ratio * **	0.04 ± 0.05	0.04 ± 0.03	0.03 ± 0.01	0.07 ± 0.10	0.04 ± 0.06	0.03 ± 0.03
Single-support time						
Paretic (% gait cycle) * **	0.28 ± 0.08	0.33 ± 0.06	0.34 ± 0.05	0.31 ± 0.07	0.33 ± 0.05	0.33 ± 0.04
Non-paretic (% gait cycle) *	0.32 ± 0.06	0.36 ± 0.05	0.36 ± 0.04	0.36 ± 0.05	0.37 ± 0.05	0.36 ± 0.04
Symmetry ratio * **	0.05 ± 0.05	0.03 ± 0.04	0.03 ± 0.03	0.04 ± 0.03	0.04 ± 0.03	0.03 ± 0.03
Functional gait tasks						
10-Meter Walk Test (m/s) * **	0.61 ± 0.35	0.86 ± 0.38	1.07 ± 0.27	0.76 ± 0.38	0.95 ± 0.38	1.07 ± 0.40
6-Minute Walk Test (m) * **	220 ± 149	301 ± 163	398 ± 119	247 ± 130	343 ± 147	383 ± 138
Functional Gait Assessment * **	14.7 ± 5.7	19.5 ± 4.8	23.6 ± 5.4	15.9 ± 5.8	21.7 ± 5.2	21.7 ± 5.3
Timed Up and Go test (s) * **	23.1 ± 15.0	17.0 ± 14.4	11.4 ± 6.1	19.5 ± 11.8	14.1 ± 7.6	12.4 ± 6.4
Clinical scores						
Fugl Meyer Assessment – leg score * **	24.2 ± 4.6	26.4 ± 5.0	28.9 ± 4.1	23.4 ± 6.8	28.9 ± 4.1	26.8 ± 5.5
Motricity Index – leg score * **	63.9 ± 17.0	77.0 ± 13.7	86.2 ± 13.2	62.5 ± 26.4	71.8 ± 24.6	72.5 ± 22.2

*significant *Time* effect T0 vs T1 ($p \leq 0.05$); **significant *Time* effect T0 vs T2 ($p \leq 0.05$); † significant *Group x Time* interaction T0 vs T1 ($p \leq 0.05$); ‡ significant *Group x Time* interaction T0 vs T2 (p-value ≤ 0.05);
Functional Gait Assessment: range 0-30; Fugl Meyer Assessment – leg score: range 0–34; Motricity Index – leg score: range 0-100.

Individual training goals

Participants with a pre-defined training goal aimed at foot clearance (n = 12) did not show a significant difference in the change in peak knee flexion between the robotic and conventional training group from T0 to T1 ($p = 0.055$), but this parameter reached significance in favor of the robotic training group when comparing T0 with T2 ($p = 0.016$, effect size $r = 0.55$) (see Table 3 and Supplementary Table S2). Participants with a pre-defined training goal aimed at knee stability (n = 13) did not show significant differences in the change in maximal knee extension velocity of the paretic relative to the non-paretic leg between groups for either time interval (T0 vs T1, $p = 0.570$; T0 vs T2, $p = 0.796$). Six participants had a primary training goal aimed at improving limb loading and one participant at improving foot prepositioning. These subgroups were considered too small to allow statistical sub-analysis.

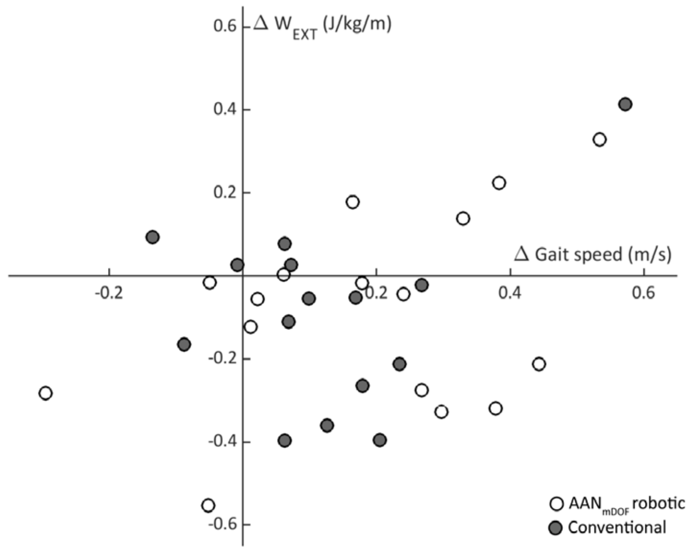

Figure 4. Individual change in gait speed plotted against the individual change in external mechanical work from T0 to T1, for individuals in the AAN$_{mDOF}$ robotic and conventional gait training groups. Only data of individuals who completed both assessments at T0 and T1 are shown (n = 31). Positive change indicates an increased value of the variable at T1 relative to T0. Preferably, participants would be in the right lower quadrant (increased gait speed / decreased external work) or lower part of the right upper quadrant (increased gait speed / slightly increased external work).

Table 3. Medians (ranges) of gait kinematics related to individual pre-defined training goals for the AAN$_{mDOF}$ robotic and conventional gait training groups before (T0), immediately after (T1), and four months after (T2) the intervention period.

	AAN$_{mDOF}$ robotic			Conventional		
	T0	T1	T2	T0	T1	T2
Foot clearance	n = 6	n = 6	n = 6	n = 6	n = 6	n = 6
Peak knee flexion (°) **	31.6 (11.4-54.3)	47.9 (16.3-60.0)	52.4 (16.9-59.5)	42.1 (29.5-56.6)	36.5 (22.4-64.1)	33.9 (20.7-53.5)
Knee stability	n = 6	n = 5	n = 3	n = 7	n = 7	n = 6
Difference in paretic vs non-paretic maximum knee extension velocity (°/s)	-13.7 (-76.2-27.5)	-9.0 (-22.9-37.4)	-20.9 (-67.3-32.7)	-25.6 (-100.6-41.3)	-34.6 (-79.3-67.1)	-7.5 (-55.3-53.0)
Limb loading	n = 4	n = 4	n = 3	n = 2	n = 2	n = 2
Single-support time symmetry ratio	0.02 (0.01-0.15)	0.01 (0-0.14)	0.01 (0-0.13)	0.04 (0.04-0.04)	0.02 (0-0.03)	0.02 (0-0.04)

**significant between group difference T0 vs T2 ($p \leq 0.05$). The individual pre-defined training goal foot prepositioning was excluded from analysis because n=1

Discussion

Our hypothesis that, in the subacute phase after stroke, six weeks of AAN$_{mDOF}$ robotic gait training would be superior to conventional gait training in terms of W_{EXT} (as a generic measure of the quality of the gait pattern) was not corroborated by the results of this study. Both the AAN$_{mDOF}$ robotic and conventional gait training groups showed equally reduced W_{EXT} one week after the intervention period, combined with similarly increased gait speed. At four months follow-up, there was a further and similar increase in gait speed in both groups, while W_{EXT} returned to baseline values. In addition, compared to baseline, most spatiotemporal parameters, all functional gait tasks and all clinical scores had similarly improved in both groups one week after the intervention and at follow-up. The AAN$_{mDOF}$ robotic gait training group showed no difference in step width one week after the intervention, in contrast to a slight increase in the conventional training group. In addition, at follow-up, paretic step length had increased only in the AAN$_{mDOF}$ robotic gait training group. Furthermore, of all patients with a predefined goal aimed at foot clearance, only those who received AAN$_{mDOF}$ robotic gait training were able to improve their maximal knee flexion after the intervention. No such subgroup differences were observed for patients with other predefined goals such as knee stability or limb loading.

Overall, our findings do not indicate a clear superior effect of AAN$_{mDOF}$ robotic gait training compared to conventional gait training during primary inpatient stroke rehabilitation. Although the conventional gait training group showed a potentially undesirable increase in step width directly after the intervention period, the change was very small (2 cm) and step width at follow-up remained similar in both groups. Additionally, the AAN$_{mDOF}$ robotic gait training group had increased their paretic step length at follow-up more than the conventional training group, but this effect was related to a shorter paretic step length at baseline in the robotic group. Indeed, both groups reached almost perfect symmetry at follow-up. Consequently, the clinical relevance of these findings is questionable. Hence, the data suggest that people after stroke recover in terms of motor impairments (clinical scores) and motor capacities (W_{EXT}, gait speed, symmetry, and functional gait tasks) independent of the type of gait training. Our findings are in line with previous studies reporting beneficial effects of AAN$_{mDOF}$ robotic gait training (*not* complemented with conventional gait training) on the over ground gait pattern and on clinical outcomes in chronic stroke survivors[44-46]. Furthermore, such AAN$_{mDOF}$ robotic gait training combined with functional electrical stimulation was not found to be superior to therapist-assisted body-weight supported treadmill training in a small group of stroke survivors[45]. Hence, the findings of our randomized controlled trial add up to the current evidence that the effectiveness of AAN$_{mDOF}$ robotic gait training is limited, but that AAN$_{mDOF}$ robotic gait training might be used as an alternative for conventional gait training.

One week after the intervention, an increase in gait speed and concurrent decrease in W_{EXT} was observed in both groups. In contrast, previous studies have shown that faster gait speed is typically associated with increased levels of W_{EXT}[26,30,31]. In line, eight of our participants had increased their gait speed and increased their W_{EXT} accordingly (see Figure 4). However, most of our participants (n=17) showed an increased gait speed and a concurrent *decrease* in W_{EXT}. This observed decrease in W_{EXT} while walking at a faster speed can be explained by reduced COM movements relative to the surroundings, suggesting that participants reduced their (compensatory) movements in the planes perpendicular to the walking direction. Taken together, these results indicate a more mechanically efficient, and better qualitative gait pattern one week after the intervention in both groups, which is supported by concurrent improvements in gait symmetry in both groups. Interestingly, at follow-up, the gait speed had further increased in both groups, however, now combined with a concurrent *increase* in W_{EXT} to baseline values. This suggests a further increase in functional gait capacity with a stabilization of mechanical efficiency and quality of the gait pattern in both groups four months after the intervention.

Although the analysis of individual training goals demonstrated mixed results, of all participants with a pre-defined goal aimed at improving foot clearance, only those who received robotic gait training had increased their peak knee flexion during swing at follow-up (+66%), whereas peak knee flexion had decreased at follow-up in those who received conventional gait training (-19%) (see Table 3). Individuals in the conventional gait training group may have relied more on compensatory pelvic hike and hip abduction ('circumduction') to ensure foot clearance[5]. Although the effect size of this subgroup difference seems to be fairly large, the statistics are based on a small group size and, thus, should be interpreted with caution. It might be that individuals in the AAN_{mDOF} robotic gait training group benefited from appropriate proprioceptive information through continuous adaption of knee joint guidance from the AAN_{mDOF} robot. Therefore, AAN_{mDOF} robotic gait training that can support specific subtasks of the gait cycle seems to have the possibility to promote gait kinematics, but further research with larger group sizes is needed to determine its effect on all prerequisites of gait.

A limitation of the present study is that the generalizability of our results is limited to people suffering from primary or recurrent unilateral supratentorial stroke with independent ambulation prior to their stroke, a minimal level of independent ambulation after their stroke, and without relevant comorbidities. As a consequence, merely 7.5% of the individuals assessed for eligibility were eventually randomized to one of the training groups. Because participants had to be able to perform the gait analysis independently, individuals with poor (dependent) ambulatory capacity were excluded. As this latter group may typically profit from mechanically assisted gait training[47], it is still relevant to investigate the effect of AAN_{mDOF} robotic gait training in those with more severely affected gait capacity after stroke. A second limitation is that the study may lack sufficient power, as the number of included participants was smaller than the calculated sample size. Nevertheless, it should be noted that the original power calculation was based on a Beta of 10%. Using a Beta of 20% would have required 36 participants. Given the current sample size of 34 participants and the absence of any trend in the *Group x Time* interaction effects, we assume that the chance of false-negative study results is very small. A third limitation is that, with regard to the gait training, the AAN_{mDOF} robotic training group ultimately received 19% more training sessions than the conventional training group. This difference in training intensity might have worked in favor of the robotic group, but the results did not show any indication of such an effect. Lastly, the calculation of W_{EXT} was based on the COM movements derived from the gait kinematics instead of integrating ground reaction forces[48]. As it was difficult for several participants to successfully hit the force plate during gait analysis, ground reaction forces could not be recorded in a sufficient number of steps to be analyzed properly. Although the use of COM movements derived from kinematics implies multiple assumptions about anthropometry, rigidity of body segments, and correct marker placement, this method still appears to be valid for calculating W_{EXT}[49].

Conclusion

AAN_{mDOF} robotic gait training was not superior to conventional gait training for improving W_{EXT}, spatiotemporal gait characteristics, functional gait tasks, or clinical scores in stroke survivors during their primary inpatient rehabilitation. However, we found some indication of a beneficial (kinematic) effect of AAN_{mDOF} robotic gait training on peak knee flexion during the swing phase in a subgroup of participants with a predefined training goal aimed at improving foot clearance.

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References

1. Bohannon RW, Andrews AW, Smith MB. Rehabilitation goals of patients with hemiplegia. Int J Rehabil Res. 1988;11(2):181-184.
2. Harris JE, Eng JJ. Goal Priorities Identified through Client-Centred Measurement in Individuals with Chronic Stroke. Physiother Can. 2004;56(3):171-176.
3. Mumma CM. Perceived losses following stroke. Rehabil Nurs. 1986;11(3):19-24.
4. Balaban B, Tok F. Gait disturbances in patients with stroke. PM & R. 2014;6(7):635-642.
5. Chen G, Patten C, Kothari DH, Zajac FE. Gait differences between individuals with post-stroke hemiparesis and non-disabled controls at matched speeds. Gait Posture. 2005;22(1):51-56.
6. Moseley A, Wales A, Herbert R, Schurr K, Moore S. Observation and analysis of hemiplegic gait: stance phase. Aust J Physiother. 1993;39(4):259-267.
7. Patterson KK, Parafianowicz I, Danells CJ, et al. Gait asymmetry in community-ambulating stroke survivors. Arch Phys Med Rehabil. 2008;89(2):304-310.
8. Olney SJ, Richards C. Hemiparetic gait following stroke. Part I: Characteristics. Gait Posture. 1996;4(2):136-148.
9. Van der Kooi E, Schiemanck SK, Nollet F, Kwakkel G, Meijer JW, Van de Port I. Falls Are Associated With Lower Self-Reported Functional Status in Patients After Stroke. Arch Phys Med Rehabil. 2017;98(12):2393-2398.
10. Durcan S, Flavin E, Horgan F. Factors associated with community ambulation in chronic stroke. Disabil Rehabil. 2016;38(3):245-249.
11. Chang WH, Kim MS, Huh JP, Lee PK, Kim YH. Effects of robot-assisted gait training on cardiopulmonary fitness in subacute stroke patients: a randomized controlled study. Neurorehabil Neural Repair. 2012;26(4):318-324.
12. Chua J, Culpan J, Menon E. Efficacy of an Electromechanical Gait Trainer Poststroke in Singapore: A Randomized Controlled Trial. Arch Physi Med Rehabil. 2016;97(5):683-690.
13. Han EY, Im SH, Kim BR, Seo MJ, Kim MO. Robot-assisted gait training improves brachial-ankle pulse wave velocity and peak aerobic capacity in subacute stroke patients with totally dependent ambulation: Randomized controlled trial. Medicine. 2016;95(41):e5078.
14. Husemann B, Muller F, Krewer C, Heller S, Koenig E. Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke. 2007;38(2):349-354.
15. Morone G, Bragoni M, Iosa M, et al. Who may benefit from robotic-assisted gait training? A randomized clinical trial in patients with subacute stroke. Neurorehabil Neural Repair. 2011;25(7):636-644.
16. Ochi M, Wada F, Saeki S, Hachisuka K. Gait training in subacute non-ambulatory stroke patients using a full weight-bearing gait-assistance robot: A prospective, randomized, open, blinded-endpoint trial. J Neurol Sci. 2015;353(1-2):130-136.
17. Van Nunen MP, Gerrits KH, Konijnenbelt M, Janssen TW, De Haan A. Recovery of walking ability using a robotic device in subacute stroke patients: a randomized controlled study. Disabil Rehabil Assist Technol. 2015;10(2):141-148.
18. Hidler J, Nichols D, Pelliccio M, et al. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair. 2009;23(1):5-13.
19. Emken JL, Benitez R, Reinkensmeyer DJ. Human-robot cooperative movement training: learning a novel sensory motor transformation during walking with robotic assistance-as-needed. J Neuroeng Rehabil. 2007;4:8.
20. Meuleman J, Van Asseldonk E, Van Oort G, Rietman H, Van der Kooij H. LOPES II--Design and Evaluation of an Admittance Controlled Gait Training Robot With Shadow-Leg Approach. IEEE Trans Neural Syst Rehabil Eng. 2016;24(3):352-363.
21. Aurich-Schuler T, Grob F, Van Hedel HJA, Labruyere R. Can Lokomat therapy with children and adolescents be improved? An adaptive clinical pilot trial comparing Guidance force, Path control, and FreeD. J Neuroeng Rehabil. 2017;14:14.
22. Duschau-Wicke A, Caprez A, Riener R. Patient-cooperative control increases active participation of individuals with SCI during robot-aided gait training. J Neuroeng Rehabil. 2010;7:43.
23. Duschau-Wicke A, Von Zitzewitz J, Caprez A, Lunenburger L, Riener R. Path control: a method for patient-cooperative robot-aided gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2010;18(1):38-48.
24. Veneman JF, Menger J, Van Asseldonk EH, Van der Helm FC, Van der Kooij H. Fixating the pelvis in the horizontal plane affects gait characteristics. Gait Posture. 2008;28(1):157-163.
25. Hidler J, Sainburg R. Role of Robotics in Neurorehabilitation. Top Spinal Cord Inj Rehabil. 2011;17(1):42-49.
26. Willems PA, Cavagna GA, Heglund NC. External, internal and total work in human locomotion. J Exp Biol. 1995;198(2):379-393.
27. Saunders JB, Inman VT, Eberhart HD. The major determinants in normal and pathological gait. J Bone Joint Surg Am. 1953;35(3):543-558.
28. Do Carmo AA, Kleiner AF, Barros RM. Alteration in the center of mass trajectory of patients after stroke. Top Stroke Rehabil. 2015;22(5):349-356.
29. Detrembleur C, Dierick F, Stoquart G, Chantraine F, Lejeune T. Energy cost, mechanical work, and efficiency of hemiparetic walking. Gait Posture. 2003;18(2):47-55.
30. Balbinot G. Walking at non-constant speeds: mechanical work, pendular transduction, and energy congruity. Scand J Med Sci Sports. 2017;27(5):482-491.
31. Cavagna GA, Thys H, Zamboni A. The sources of external work in level walking and running. J Physiol. 1976;262(3):639-657.
32. Gage JR. Gait analysis. An essential tool in the treatment of cerebral palsy. Clin Orthop Relat Res. 1993;288:126-134.
33. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scand J Rehabil Med. 1975;7(1):13-31.
34. Demeurisse G, Demol O, Robaye E. Motor evaluation in vascular hemiplegia. Eur Neurol. 1980;19(6):382-389.
35. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-699.
36. Pijfers L, De Vries LA, Messing-Peterson H. Het Utrechts Communicatie Onderzoek. 1st ed. Westervoort: Stichting Afasie Nederland; 1985.
37. Veerbeek JM, Van Wegen E, Van Peppen R, et al. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. PLoS One. 2014;9(2):e87987.
38. Zeni JA, Jr., Richards JG, Higginson JS. Two simple methods for determining gait events during treadmill and overground walking using kinematic data. Gait Posture. 2008;27(4):710-714.
39. Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J. 1985;132(8):919-923.
40. Collen FM, Wade DT, Bradshaw CM. Mobility after stroke: reliability of measures of impairment and disability. Int Disabil Stud. 1990;12(1):6-9.
41. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142-148.
42. Wrisley DM, Marchetti GF, Kuharsky DK, Whitney SL. Reliability, internal consistency, and validity of data obtained with the functional gait assessment. Phys Ther. 2004;84(10):906-918.

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43. Stoquart G, Detrembleur C, Lejeune TM. The reasons why stroke patients expend so much energy to walk slowly. Gait Posture. 2012;36(3):409-413.
44. Srivastava S, Kao PC, Kim SH, et al. Assist-as-Needed Robot-Aided Gait Training Improves Walking Function in Individuals Following Stroke. IEEE Trans Neural Syst Rehabil Eng. 2015;23(6):956-963.
45. Srivastava S, Kao PC, Reisman DS, Scholz JP, Agrawal SK, Higginson JS. Robotic Assist-As-Needed as an Alternative to Therapist-Assisted Gait Rehabilitation. Int J Phys Med Rehabil. 2016;4(5):370-377.
46. Seo JS, Yang HS, Jung S, Kang CS, Jang S, Kim DH. Effect of reducing assistance during robot-assisted gait training on step length asymmetry in patients with hemiplegic stroke: A randomized controlled pilot trial. Medicine. 2018;97(33):e11792.
47. Mehrholz J, Thomas S, Werner C, Kugler J, Pohl M, Elsner B. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2017;5(5):CD006185.
48. Cavagna GA. Force platforms as ergometers. J Appl Physiol. 1975;39(1):174-179.
49. Pavei G, Seminati E, Cazzola D, Minetti AE. On the Estimation Accuracy of the 3D Body Center of Mass Trajectory during Human Locomotion: Inverse vs. Forward Dynamics. Front Physiol. 2017;8:129.

Supplementary files

Table S1. Results of the mixed model analyses on both groups for two time intervals

	To vs T1			To vs T2		
	Time	Group	Interaction	Time	Group	Interaction
Mechanical work						
W_{EXT} (J/kg/m)	F(1,29.583)=4.680; p=0.039	F(1,29.864) =0.037; p=0.849	F(1,29.583)=0.008; p=0.930	F(1,27.835)=1.304; p=0.263	F(1,27.945)=0.018; p=0.895	F(1,27.835) =0.010; p=0.926
Spatiotemporal parameters						
Gait speed (m/s)	F(1,29.287)=20.015; p<0.001	F(1,30.015) =1.016; p=0.321	F(1,29.287)=0.619; p=0.438	F(1,28.365)=45.365; p<0.001	F(1,30.213)=0.681; p=0.416	F(1,28.365) =2.168; p=0.152
Step width (m)	F(1,29.113)=1.832; p=0.186	F(1,30.108) =0.602; p=0.444	F(1,29.113)=6.326; p=0.018	F(1,25.504)=0.013; p=0.910	F(1,30.256)=0.850; p=0.364	F(1,25.504) =4.058; p=0.055
Step length						
Paretic (m)	F(1,28.284)=29.077; p<0.001	F(1,29.570) =1.647; p=0.209	F(1,28.284)=2.504; p=0.125	F(1,26.721)=39.272; p<0.001	F(1,29.594)=0.958; p=0.336	F(1,26.721) =5.476; p=0.027
Non-paretic (m)	F(1,29.287)=41.377; p<0.001	F(1,29.972) =0.554; p=0.463	F(1,29.287)=0.594; p=0.447	F(1,28.695)=38.621; p<0.001	F(1,29.938)=0.521; p=0.476	F(1,28.695) =0.676; p=0.418
Symmetry ratio	F(1,29.564)=4.228; p=0.049	F(1,29.893) =0.565; p=0.458	F(1,29.564)=1.672; p=0.206	F(1,30.076)=6.1272; p=0.019	F(1,30.085)=0.876; p=0.357	F(1,30.076) =1.035; p=0.317
Single-support time						
Paretic (% gait cycle)	F(1,29.904)=20.695; p<0.001	F(1,30.098) =0.960; p=0.335	F(1,29.904)=2.786; p=0.106	F(1,25.735)=27.566; p<0.001	F(1,29.148)=0.809; p=0.376	F(1,25.735) =3.768; p=0.063
Non-paretic (% gait cycle)	F(1,29.590)=9.5382; p=0.005	F(1,30.114) =2.164; p=0.152	F(1,29.590)=1.633; p=0.211	F(1,29.496)=3.408; p=0.075	F(1,30.098)=1.711; p=0.201	F(1,29.496) =2.210; p=0. 148
Symmetry ratio	F(1,29.925)=6.471; p=0.016	F(1,30.114) =0.032; p=0.859	F(1,29.925)=3.819; p=0.060	F(1,25.113)=7.102; p=0.013	F(1,28.395)=0.120; p=0.732	F(1,25.113) =0.217; p=0.645
Functional gait tasks						
10-Meter Walk Test (m/s)	F(1,29.043)=49.900; p<0.001	F(1,29.950) =1.066; p=0.310	F(1,29.0.43)=0.811; p=0.375	F(1,25.658)=81.039; p<0.001	F(1,29.998)=1.101; p=0.302	F(1,25.658) =0.675; p=0.419
6-Minute Walk Test (m)	F(1,29.038)=59.246; p<0.001	F(1,29.959) =0.585; p=0.450	F(1,29.038)=1.367; p=0.252	F(1,25.332)=111.055; p<0.001	F(1,29.782)=0.187; p=0.668	F(1,25.332) =0.197; p=0.661
Functional Gait Assessment	F(1,29.053)=61.375; p<0.001	F(1,29.834) =1.016; p=0.321	F(1,29.053)=1.029; p=0.319	F(1,26.189)=78.709; p<0.001	F(1,30.034)=0.000; p=0.991	F(1,26.189) =2.156; p=0.154
Timed Up and Go test (s)	F(1,28.779)=23.613; p<0.001	F(1,29.683) =0.792; p=0.381	F(1,28.779)=0.112; p=0.740	F(1,23.328)=31.287; p<0.001	F(1,27.521)=0.663; p=0.422	F(1,23.328) =0.076; p=0.785
Clinical scores						
Fugl Meyer Assessment – leg score	F(1,29.225)=19.525; p<0.001	F(1,30.088) =0.109; p=0.743	F(1,29.225)=0.095; p=0.760	F(1,25.070)=27.119; p<0.001	F(1,28.953)=0.303; p=0.586	F(1,25.070) =0.080; p=0.780
Motricity Index – leg score	F(1,29.065)=23.784; p<0.001	F(1,29.892) =0.090; p=0.767	F(1,29.065)=0.121; p=0.731	F(1,25.579)=35.326; p<0.001	F(1,29.727)=0.610; p=0.441	F(1,25.579) =2.439; p=0.131

Table S2. Results of the Mann-Whitney U analyses of gait kinematics related to individual pre-defined training goals in both groups for two time intervals

	T0 vs T1	T0 vs T2
Foot clearance		
Peak knee flexion during the swing phase	U=6.000; z=-1.922; p=0.055	U=3.000; z=-2.402; p=0.016
Knee stability		
Difference in paretic vs non-paretic maximum knee extension velocity during the stance phase	U=14.000; z=-0.568; p=0.570	U=8.000 ;z=-0.258; p=0.796

Chapter 4

Effectiveness of rehabilitation interventions to improve paretic propulsion in individuals with stroke – a systematic review

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Abstract

Background
Stroke survivors often show reduced walking velocity and gait asymmetry. These gait abnormalities are associated with reduced propulsion of the paretic leg. This review aimed to provide an overview of the potential effectiveness of post-stroke rehabilitation interventions to improve paretic propulsion, ankle kinetics and walking velocity.

Methods
A systematic search was performed in Pubmed, Web of Science, Embase, and Pedro. Studies were eligible if they reported changes in propulsion measures (impulse, peak value and symmetry ratios) or ankle kinetics (moment and power) following intervention in stroke survivors (group size ≥ 10). Study selection, data extraction and quality assessment were performed independently by two authors.

Results
A total of 28 studies were included, of which 25 studies applied exercise interventions, two studies focused on surgical interventions, and one on non-invasive brain stimulation. The number of high-quality trials was limited (N = 6; score Downs and Black scale ≥ 19). Propulsion measures were the primary outcome in eight studies. In general, mixed results were reported with 14 interventions yielding improvements in propulsion and ankle kinetics. In contrast, gains in walking velocity were observed in the vast majority of studies (N = 20 out of 23).

Conclusions
Interventions that yielded gains in propulsion appeared to have in common that they challenged and/or enabled the utilization of latent propulsive capacity of the paretic leg during walking. Walking speed generally increased, regardless of the observed change in propulsion, suggesting the use of compensatory mechanisms. Findings should, however, be interpreted with some caution, as the evidence base for this emerging focus of rehabilitation is limited.

Introduction

Improvement of the walking pattern and walking velocity are major rehabilitation goals for individuals post stroke[1]. Approximately 64% of all stroke survivors admitted for inpatient rehabilitation achieve independent walking before being discharged home[2]. Yet, people after stroke often experience persistent gait abnormalities, such as reduced walking velocity[3], impaired balance control[4] and gait asymmetry[5,6]. In addition, 'drop foot', 'stiff-knee gait' and circumduction[7] are frequently observed following stroke. These gait abnormalities contribute to lower levels of community ambulation and reduced quality of life[8].

Several post-stroke gait abnormalities, like reduced knee flexion during swing[9], reduced step-length symmetry[10], and reduced walking velocity[11] may be (partly) due to impaired propulsion of the paretic leg. Generation of propulsive forces is one of the essential requirements for walking[12]. Propulsion contributes to the forward progression of the body and can be derived from the anterior-posterior ground reaction force during walking. The two most important factors associated with the production of propulsion are the ankle plantarflexion moment and the posterior orientation of the center of pressure relative to the position of the center of mass[13]. In stroke survivors, the generated propulsive forces are generally lower than those reported in healthy adults[5], and the propulsive force of the paretic limb is often smaller than that of the non-paretic leg[14]. Accordingly, interventions targeting paretic propulsion have the potential to improve the walking pattern post stroke.

In the past years, an increasing number of studies have been published that assessed changes in paretic propulsion in stroke survivors following interventions. The primary objective of this systematic review was to provide an overview of the potential effectiveness of these rehabilitation interventions for improving propulsion outcomes and ankle kinetics during walking. As improvements in paretic propulsion may result in increased walking velocity, the secondary aim of this review was to assess the effectiveness of these interventions on walking velocity.

Methods

This systematic review was conducted following the PRISMA statement[15]. Since the PRISMA statement is designed for systematic reviews and meta-analysis of intervention studies, we only addressed the items related to systematic reviews.

Eligibility criteria
To be included in the review process, each study had to meet the following criteria:

1) Type of participants: Adult participants (> 18 years of age) suffering from an ischemic or hemorrhagic stroke in the acute (≤ one week post stroke[16]), subacute (first week until six months post stroke[16]) or chronic phase (> six months post stroke[16]). Studies were excluded if the study was conducted in the (sub)acute phase after stroke, without inclusion of a control group, as uncontrolled study designs in this post-stroke stage do not allow distinguishing interventions effects from changes due to spontaneous recovery. Studies were only considered for inclusion if data of 10 or more people with stroke were reported.

2) Type of intervention: Studies involving single or repeated intervention sessions, without restrictions with regard to the type or intensity of the intervention.
3) Comparison: Studies comparing the pre- to post-intervention changes in outcomes within and/or between each intervention group. Studies were excluded if the changes in outcomes were not statistically tested, or if the pre- and post-intervention measurement were conducted under different circumstances (for example, when an ankle-foot orthosis was worn during the post-intervention measurement but not during the pre-intervention measurement).
4) Outcome measures: Propulsion of the paretic leg during walking measured as primary or secondary outcome of the study. Propulsion measures included:
   a. Propulsive impulse, defined as the time integral of the positive anterior ground reaction force of the paretic leg during the stance phase of gait.
   b. Propulsion symmetry, defined as the propulsive impulse of the paretic leg divided by the sum of the propulsive impulse of the paretic and non-paretic leg.
   c. Peak propulsive force, defined as the maximal positive anterior ground reaction force of the paretic leg during the stance phase of gait.

   In order to provide a complete overview of potentially effective interventions, we chose to also include studies reporting ankle kinetics, as these measures are related to propulsion[13,17]:
   a. Peak ankle moment, defined as the maximum ankle plantarflexion moment during the stance phase of gait.
   b. Peak ankle power, defined as the maximum value of the cross product of the ankle plantarflexion moment and the angular velocity of the paretic leg during the stance phase of gait.

   Electromyographic activity of the calf muscles, and range of motion of the lower limb joints were not considered as outcome measures of propulsion.
5) Language: Studies had to be written in English, German, or the Dutch language.

No restrictions on publication date were imposed.

Information sources

Studies were selected from electronic database searches and additional scanning of the article reference lists. The electronic database search was applied to Pubmed (1809 – Present), Web of Science (1945 – Present), Embase (1974 – Present), and the Pedro database (1929 – Present). The literature search was conducted by the first author (JA) on May 8th 2019. Studies were excluded from the review if no full text paper was available online or provided upon author request.

Search Strategy

The following search terms were used to select studies from the Pubmed database:

(cerebrovascular disorders [mesh] OR paresis [mesh] OR hemiplegia [mesh] OR stroke OR cva OR cerebrovascular) AND (rehabilitation [mesh] OR exercise [mesh] OR therapeutics [mesh] OR intervention OR training OR therapy OR rehabil) AND (walking [mesh] OR lower extremity [mesh] OR walking OR gait) AND (propulsion OR propulsive OR ground reaction force OR GRF OR (kinetic* AND force))*

A detailed description of the search strategies used in all different databases is presented in Appendix 1.

Study selection

First, duplicates were manually removed from the search based on title, journal, and author information. Second, title and abstract of the retrieved studies were screened for eligibility. Assessment of eligibility was performed independently by two reviewers (JA, BG). If a study had the potential to be included, the full text article was screened before definitive inclusion. Reference lists and citations of the selected studies were checked to identify additional relevant studies. Disagreement between reviewers was resolved by consensus or after consulting a third assessor (VW).

Data collection

Data were extracted from the studies by reviewer 1 (JA) and then checked by reviewer 2 (BG). Disagreement between reviewers was resolved by consensus. Four authors were contacted to request additional information regarding the outcome data, of which two authors responded to our request. None provided additional numerical data. The following information was extracted from the included studies:
1) Author and year of publication
2) Study design
3) Participant characteristics: Number of post-stroke participants, age and time post stroke in the experimental and (if applicable) control group.
4) Type of intervention: Type, duration and frequency of the applied rehabilitation intervention and (if applicable) control treatment. Interventions were either classified as ‘Exercise interventions’ when the intervention included walking or other physical exercises, or as ‘Other interventions’ when the intervention did not primarily involve physical exercises.
5) Type of outcome measures: Type of propulsion or ankle kinetics measures investigated.
6) Effect of intervention on propulsion or ankle kinetics measures: Mean difference in each propulsion or ankle kinetics measure between the pre and post measurement. If available, the change in each outcome measure was extracted between the pre and follow-up measurement and between experimental groups. Mean differences were categorized as statistically significant increase (+), significant decrease (–), or non-significant change (=). If outcome parameters were not included in the study protocol, or data was not provided after author request, the intervention effects were expressed as ‘Not applicable’ (NA) or ‘Not reported’ (NR), respectively. For controlled studies conducted in the (sub)acute phase after stroke, changes in propulsion or ankle kinetics measures between the pre and post or follow-up measurement within each group are shown in grey in the tables, as these changes may be (partly) due to spontaneous recovery. Studies that included a propulsion measure as the primary outcome are shown in bold in the tables.
7) Effect of intervention on walking velocity: Walking velocity was used as secondary outcome measure in this review, defined as the self-selected, comfortable walking speed. If available, the mean difference in walking velocity between the pre and post measurements was extracted. Mean differences were categorized as statistically significant increase (+), significant decrease (–), or non-significant change (=). If walking velocity was not measured according to the study protocol, or data was not provided after author request, the intervention effect was expressed as ‘Not applicable’ (NA) or ‘Not reported’ (NR), respectively.

Quality assessment

To globally assess the quality of the included studies, the Downs and Black scale[18] was used. This scale consists of 27 items which provide insight into the reporting quality, external validity, internal validity (bias and confounding) and power. Item 27 was slightly modified, to score the availability of a power analysis (see Appendix 2 for the complete scale). Scores ranged from 0 to 28, and a study with a total score of 19 or more (> 66%) was considered to be of high quality[19]. Assessment of study quality was performed independently by two reviewers (JA, BG), with disagreement between reviewers being resolved by consensus or after consulting a third assessor (VW).

Results

Study selection

The search in the electronic databases identified a total of 1061 citations, of which 659 unique citations remained after adjusting for duplicates. A total of 28 studies met the eligibility criteria and were included in this review[11,20-46]. An overview of the selection procedure is provided in the flowchart (Figure 1).

Study characteristics

Characteristics of the 28 included studies are shown in Table 1. They consisted of 12 randomized controlled trials[22-24,29,31,35-37,40,42,45,46], two randomized cross-over trial[38,44], one non-randomized controlled trial[30], one non-randomized cross-over trial[33], seven pre-post studies without follow-up[11,28,32,34,39,41,43], and five pre-post studies with follow-up[20,21,25-27]. Overall, 25 studies were classified as 'Exercise interventions'[11,20-24,27-43,45,46], of which eight studies reported propulsion as a primary outcome measure[11,20,27,29,30,32,34,39]. Three studies were classified as 'Other interventions'[25,26,44], of which none reported propulsion as a primary outcome. Eight studies consisted of single-session training interventions[22-24,32-34,38,44], 18 studies involved interventions with multiple training sessions[11,20,21,27-31,35-37,39-43,45,46], and two studies concerned surgical interventions[25,26]. The number of included participants ranged from 10[44] to 177[25], with 26 studies being performed in the chronic phase[11,20-34,36-39,41-46] and two studies in the subacute phase after stroke[35,40]. Outcome measures for propulsion or ankle kinetics varied across studies, with peak propulsive force being reported most frequently (N = 11), followed by propulsive impulse (N = 8), peak ankle plantarflexion moment (N = 8), peak ankle plantarflexion power (N = 8) and propulsion symmetry (N = 6). Effects on walking velocity were reported in 23 studies[11,20-31,35-37,39-43,45,46].

Quality assessment

Results of the quality assessment according to the Downs and Black scale are shown in Table 2. Six studies, which were all randomized controlled trials, were classified as having a high quality[31,35-37,40,46]. More than 90% of all studies (N ≥ 26) clearly described the main outcome (item 2), patient characteristics (item 3), intervention (item 4) and main findings (item 6). Regarding the external validity, items concerning the representativeness of the study sample (items 11 and 12) could not be judged for any of the studies.

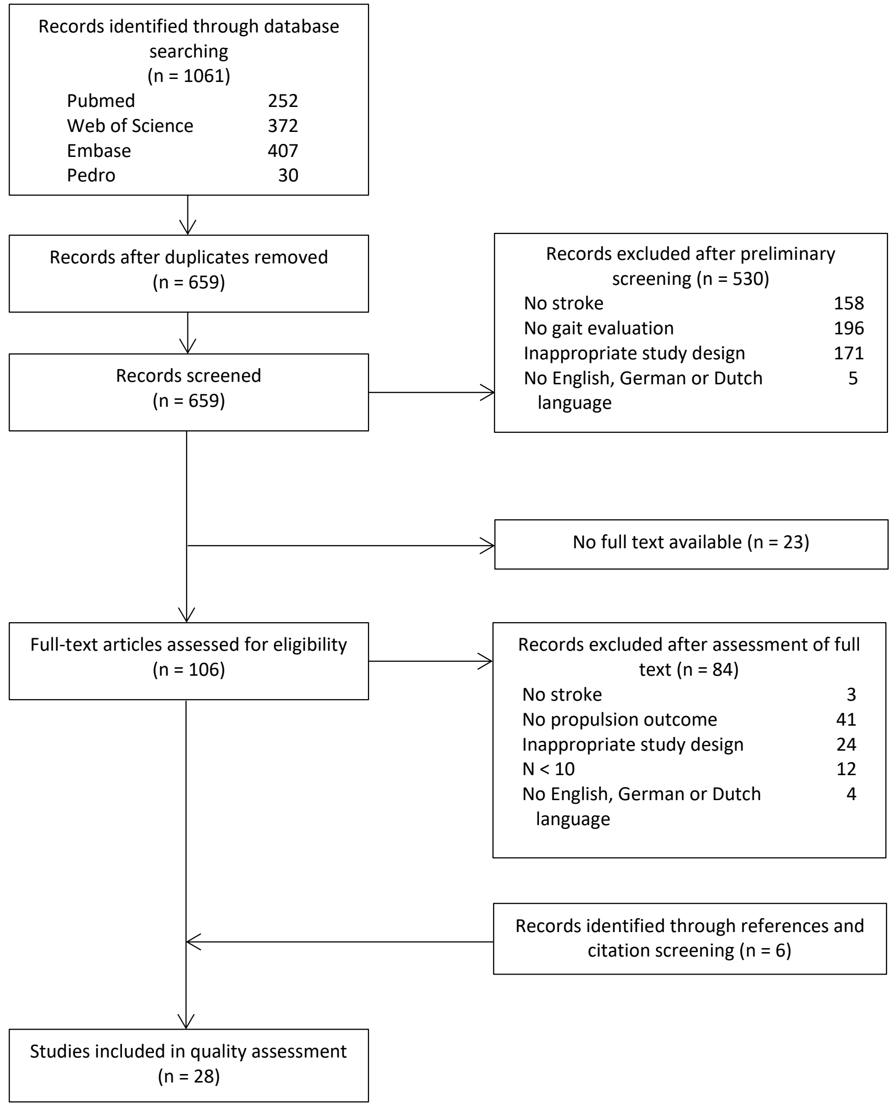

Figure 1. Flowchart.

Table 1. Characteristics of the studies included in this review. Detailed descriptions of the study population, intervention and outcome measures on propulsion, ankle kinetics and walking velocity are reported. Studies that included a propulsion measure as the primary outcome are shown in bold. Data is only reported for stroke survivors who participated in the experimental (E) or control (C) group. Outcomes are categorized as significant increase (+), significant decrease (-), or non-significant change (=) between the pre- and post-measurement, between the pre- and follow-up measurement, and between the experimental and control group. For studies conducted in the subacute phase after stroke, the outcomes between the pre- and post- or follow-up measurement are shown in grey. Apart from propulsion symmetry, the propulsion measures and ankle kinetics are solely reported for the paretic limb. Study quality is assessed with the Downs and Black scale. Detailed information about the Downs and Black scale can be found in Appendix 2. Time since stroke is reported in days (d.), weeks (wk.), months (mo.), or years (yr.).

	Type of intervention	Study			Population			Intervention		Outcomes				Velocity outcomes
		Author	Design	High study quality	N	Age in years (mean (SD))[a]	Time since stroke (mean (SD))[a]	Single session, training or surgery	Description and duration	Propulsion measures *Ankle kinetics*	Change pre-post	Change pre-follow up	Group comparison	Change pre-post
Exercise	Treadmill gait training	Mao et al 2015 [35]	RCT	Yes	24	E: 59.6 (9.2) C: 60.8 (10.7)	E: 49.3 d. (19.5) C: 47.7 d. (16.8)	Training	3 weeks E) body weight supported treadmill training or C) conventional gait training (5 times a week, 20-40 min)	*Peak ankle moment*	= (E) = (C)	NA	NA	+ (E) = (C)
		Bonnyaud et al 2013 [22]	RCT	No	26	E: 52.5 (12.3) C: 47.7 (9.8)	E: 4.2 yr. (3.3) C: 6.2 yr. (4.1)	Single session	Single session of E) treadmill training or C) overground training (20 min)	Peak propulsive force	=	+ (20 min.)	E = C	+
		Combs et al 2012 [27]	Pre-post	No	15	59.9 (11.2)	3.8 yr. (3.2)	Training	8 weeks body weight supported treadmill training (3 times a week, 20 min)	Propulsion symmetry Propulsive impulse	= =	= (6 mo.) = (6 mo.)	NA NA	+
		Routson et al 2013 [41]	Pre-post	No	27	57.3 (13.2)	19.0 mo. (13.0)	Training	12 weeks body weight supported treadmill training with manual support (3 times a week, 20 min) followed by overground walking (10-20 min)	Propulsion symmetry	=	NA	NA	+
		Lewek et al 2018 [34]	Pre-post	No	10	60 -16	105 mo. (127)	Single session	Single session of walking on a treadmill against an impeding force applied to the body's center of mass (3 min)	Propulsive symmetry Propulsive impulse Peak propulsive force	+ + +	NA NA NA	NA NA NA	NA
		Betschart et al 2018 [21]	Pre-post	No	12	53.3 (8.7)	25.1 mo. (23.5)	Training	2 weeks error-augmentation-based split belt treadmill walking with the leg with the shorter steplength walking on the faster belt (2-3 times a week, 20 min)	*Peak ankle moment*	=	=	NA	+
		Lauziere et al 2014 [33]	Cross-over	No	20	49.3 (13.2)	> 6 mo.	Single session	Single session of split belt treadmill walking at comfortable speed, with E1) paretic leg on faster belt and E2) non-paretic leg on faster belt (6 min)	*Peak ankle moment*	- (E1) + (E2)	NA	E1 < E2	NA
	Gait training with functional electrical stimulation	Sheffler et al 2015 [42]	RCT	No	110	E: 52.8 (12.2) C: 53.2 (10.1)	E: 44.7 mo. (97.5) C: 44.9 mo. (79.2)	Training	12 weeks E) training with a surface peroneal nerve stimulator (5 week, 2 times a week, 60 min & 7 week, 3 times a week, 60 min) or C) conventional care	Peak propulsive force *Peak ankle power*	+ +	= (12 wk.) + (24 wk.) + (12 wk.) + (24 wk.)	E = C E = C	+
		Awad et al 2014 [20]	Pre-post	No	13	61 (8.3)	3.2 yr. (3.1)	Training	12 weeks training at fast speed with FES delivered to both dorsal- and plantarflexors (3 times a week, 30 min)	Propulsion symmetry Propulsive impulse Peak propulsive force	+ + +	+ (3 mo.) = (3 mo.) + (3 mo.)	NA NA NA	+
		Hsiao et al 2016 [11]	Pre-post	No	45	58.3 (11.8)	4.5 yr. (6.5)	Training	12 weeks training at E1) fastest speed or E2) fast speed with FES delivered to both dorsal- and plantarflexors or C) self-selected speed (3 times a week, 36 min)	Peak propulsive force	+ (score E1, E2 & C combined)	NA	NR	+ (score E1, E2 & C combined)
		Reisman et al 2013 [39]	Pre-post	No	13	61 (8.3)	38.7 mo. (35.2)	Training	12 weeks treadmill training at fast speed with FES delivered to both dorsal- and plantarflexors (3 times a week, 30 min)	Propulsive impulse Peak propulsive force	+ (pre-4 wk.) = (4-12 wk.) + (pre-4 wk.) = (4-12 wk.)	NA NA	NA NA	+
		Kesar et al 2015 [32]	Pre-post	No	13	61.3 (9.6)	29.1 mo. (29.0)	Single session	Single session of walking at fast speed with FES delivered to both dorsal- and plantarflexors (30 min)	Propulsive impulse Peak propulsive force	+ +	NA NA	NA NA	NA

Type of intervention	Study			Population			Intervention		Outcomes				Velocity outcomes
	Author	Design	High study quality	N	Age in years (mean (SD))[a]	Time since stroke (mean (SD))[a]	Single session, training or surgery	Description and duration	Propulsion measures *Ankle kinetics*	Change pre-post	Change pre-follow up	Group comparison	Change pre-post
	Palmer et al 2017 [38]	Randomized cross-over	No	20	59.5 (12.0)	42 mo -35	Single session	Single session of walking at self-selected speed E1) with or E2) without FES delivered to both dorsal- and plantarflexors (30 min)	*Peak ankle moment*	= (E1) = (E2)	NA	NA	NA
Gait training according to modified constraint induced movement therapy	Bonnyaud et al 2013 [23]	RCT	No	60	50.3 (13.1)	5.7 yr. (6.3)	Single session	Single session of E1) overground training with mass attached to the nonparetic ankle, C1) overground training without mass, E2) treadmill training with mass attached to the nonparetic ankle or C2) treadmill training without mass (20 min)	Peak propulsive force	=	= (20 min.)	E1 = C1 E2 = C2	=
	Bonnyaud et al 2014 [24]	RCT	No	26	E: 52.1 (13.8) C: 49.1 (9.5)	E: 7.8 yr. (11.8) C: 5.5 yr. (4.7)	Single session	Single session of E) Lokomat constraint gait training or C) Lokomat conventional gait training (20 min)	Peak propulsive force	=	+ (20 min.)	E = C	+
	Hase et al 2011 [30]	Non RCT	No	22	E: 60.1 (13.0) C: 62.3 (9.2)	E: 36.4 mo. (25.1) C: 44.1 mo. (29.4)	Training	3 weeks E) prosthetic gait training or C) treadmill training (3-5 times a week, 10-15 min)	Propulsive impulse	NR	NA	E > C	C = E
Gait training with robotics	**Forrester et al 2016 [29]**	RCT	No	26	E: 59.5 (3.6) C:56.8 (3.2)	E: 37.4 mo. (10.4) C:34.0 mo. (6.8)	Training	6 weeks E) treadmill-integrated ankle robotics training or C) seated ankle robotics training (3 times a week, 60 min)	Propulsive impulse	+ (E) = (C)	+ (E, 6 wk.) = (C, 6 wk.)	E > C	+ (E) = (C)
	Yeung et al 2018 [46]	RCT	Yes	19	E: 54.2 (13.0) C: 61.2 (10.6)	E: 4.4 yr. (2.5) C: 6.0 yr. (4.5)	Training	5 weeks of overground gait training with E) a robot-assisted ankle foot orthosis assisting dorsiflexion during overground walking and a combination of plantar- and dorsiflexion during stair climbing or C) the ankle foot orthosis without robot assistance (2-4 times a week, 30-60 min)	Peak propulsive force	= (E) = (C)	NA	E = C	+ (E) = (C)
	De Luca et al 2018 [28]	Pre-post	No	12	62.75 (12.29)	6.41 yr. (4.39)	Training	5-7 weeks of robot-assisted training with an endpoint robot (3 times a week, 45 min)	*Peak ankle power*	+	NA	NA	+
Movement training with feedback	Mirelman et al 2010 [37]	RCT	Yes	18	62 (range 41-75)	>2 yr.	Training	4 weeks ankle movement training E) with virtual reality or C) without virtual reality (3 times a week, 60 min)	*Peak ankle moment* *Peak ankle power*	NR NR	NR (3 mo.) NR (3 mo.)	E > C (BF) E = C (SH) E > C (BF) E = C (SH)	+ (E) = (C)
	Jonsdottir et al 2010 [31]	RCT	Yes	20	E: 61.6 (13.1) C: 62.6 (9.5)	E: 5.9 yr. (10.5) C: 1.8 yr. (0.9)	Training	7 weeks of overground gait training with E) task-oriented EMG biofeedback recorded from the gastrocnemius lateralis or C) conventional rehabilitation (3 times a week, 45 min)	*Peak ankle power*	+ (E) = (C)	+ (E) = (C)	NA	+ (E) = (C)
Strength and conditioning training	Milot et al 2013 [36]	RCT	Yes	30	E: 58.5 (14.9) C: 54.7 (14.6)	E: 56.9 mo. (43.8) C: 85.5 mo. (111.9)	Training	6 weeks task-specific isokinetic strengthening program of the E) affected lower-limb muscles C) affected upper-limb muscles (3 times a week, 60-90 min)	*Peak ankle power*	= (E) = (C)	NA	NA	+ (E) + (C)
	Teixeira-Salmela et al 2001 [43]	Pre-post	No	13	67.7 (9.2)	7.7 yr. (9.4)	Training	10 weeks muscle strength and physical conditioning program (3 times a week, 60-90 min) with additional home-exercises (3 times a week)	*Peak ankle moment* *Peak ankle power*	= =	NA NA	NA NA	+

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	Type of intervention	Study: Author	Study: Design	Study: High study quality	Population: N	Population: Age in years (mean (SD))[a]	Population: Time since stroke (mean (SD))[a]	Intervention: Single session, training or surgery	Intervention: Description and duration	Outcomes: Propulsion measures *Ankle kinetics*	Outcomes: Change pre-post	Outcomes: Change pre-follow up	Outcomes: Group comparison	Velocity outcomes: Change pre-post
	Balance training	Yavuzer et al 2006 [45]	RCT	No	41	E: 59.8 (11.6) C: 62.1 (12.0)	E: 11.1 mo. (24.6) C: 5.5 mo. (3.5)	Training	8 weeks E) conventional rehabilitation (5 times a week, 2-5 h/day) combined with 3 weeks balance training (5 times a week, 15 min/day) or C) conventional rehabilitation (5 times a week, 2-5 h/day)	*Peak ankle moment*	= (E) = (C)	NA	E = C	=
	Training with technology	Richards et al 2004 [40]	RCT	Yes	63	E: 62.9 (12) C: 60.7 (12)	52.0 d. -22 52.6 d. -18	Training	8 weeks of E) task-oriented gait training using rehabilitation technology such as treadmills, isokinetic dynamometers or limb load monitors or C) conventional rehabilitation (5 times a week, 60 min)	*Peak ankle power*	+ (E) + (C)	NA	E = C	+ (E) + (C)
Other	Surgical elongation or transfer of the calf muscle-tendon complex	Carda et al 2009 [25]	Pre-post	No	177	49.7 (14.0)	5.6 yr. (7.5)	Surgery	Surgical correction of equinovarus foot deformity	Propulsion symmetry Peak propulsive force *Peak ankle moment* *Peak ankle power*	NA NA NA NA	+ (1 yr.) + (1 yr.) - (1 yr.) - (1 yr.)	NA NA NA NA	+
		Carda et al 2010 [26]	Pre-post	No	29	E1: 51.2 (range 32.4-70.4) E2: 50.3 (range 20-67)	E1: 6.8 yr. (range 1.6-13.7) E2: 5.1 yr. (range 1.2-10.3)	Surgery	Surgical correction of equinovarus foot deformity using E1) extensor hallucis longus transfer or E2) split transfer of the tibialis anterior tendon	Propulsion symmetry	NA	+ (E1, 1 yr.) + (E2, 1 yr.)	E1 = E2	+
	Transcranial direct current stimulation	Van Asseldonk & Boonstra 2016 [44]	Randomized cross-over	No	10	58.0 (11.1)	44.7 mo. (35.8)	Single session	Single session of E1) unihemispheric tDCS, E2) dual hemispheric tDCS and C) sham stimulation (10 min, each condition performed 1 week apart)	Propulsive impulse	= (E1) = (E2) = (C)	= (E1, 45 min.) = (E2, 45 min.) = (C, 45 min.)	E1 = E2 = C	NA

Abbreviations: electromyography (EMG), functional electrical stimulation (FES), transcranial direct current stimulation (tDCS), not applicable (NA), not reported (NR), walking barefoot (BF), walking with shoes and orthotics (SH).
[a] Unless stated otherwise

Exercise interventions

Treadmill gait training

Seven studies investigated the effect of treadmill training on paretic propulsion[22,27,34,41] or ankle kinetics[21,22,27,33-35,41], using body weight supported treadmill training[27,35,41], training on a split-belt treadmill[21,33], regular treadmill training[22], or treadmill walking with an impeding force applied to the pelvis[34]. Two studies were randomized controlled trials[22,35]. In two studies propulsion was measured as the primary outcome[27,34]. Six studies were performed in the chronic phase[21,22,27,33,34,41] and only one study was performed in the subacute phase after stroke[35]. Three studies evaluated a single session of gait training[22,33,34] and four studies evaluated multiple training sessions[21,27,35,41].

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Propulsion measures did not differ between pre and post intervention in two studies involving repeated sessions of body weight supported treadmill training[27,41]. Significant improvements in propulsion measures were only observed in studies involving a single training session that did not include body weight support . A single session of treadmill walking with a backward-oriented impeding force applied to the pelvis improved propulsive symmetry, propulsive impulse and peak propulsive force[34]. A single session of regular treadmill training without body weight support also showed improvements in peak propulsive force, but this effect was only evident at 20 minutes retention and not directly following the intervention[22]. There was, however, no superior gain in propulsion following regular treadmill compared to overground gait training, as both interventions resulted in similar effects on paretic propulsion[22].

Neither for ankle kinetics[35] nor for propulsion measures[27,41], there was any effect of repeated sessions of body weight supported treadmill training. In addition, split-belt treadmill training with the leg with the shortest step length walking on the fast belt did not affect ankle kinetics[21]. However, a single session of six minutes split-belt treadmill training with the non-paretic leg walking on the fast belt did yield improvements in peak ankle moment[33].Despite the varying effects of the interventions on propulsion and ankle kinetics, walking velocity increased in five studies[21,22,27,35,41].

Gait training with functional electrical stimulation

Six studies examined the effect of functional electrical stimulation (FES) on propulsion measures[11,20,32,39,42] or ankle kinetics[38,42] in chronic stroke survivors, applying stimulation to the peroneal nerve during walking at a comfortable velocity[42] or to both ankle dorsiflexors and plantarflexors during walking at a comfortable[38] or fast velocity[11,20,32,39]. Two studies evaluated the training effect after a single session[32,38], whereas four studies evaluated the effect after multiple training sessions[11,20,39,42], of which one study involved a randomized controlled trial[42]. Except for the studies of Sheffler et al[42] and Palmer et al[38], propulsion was measured as the primary outcome in all FES studies.

Five out of the six studies reported improvements in paretic propulsion immediately after single[32] or multiple training sessions with FES compared to pre intervention[11,20,39,42], four of which combined FES with walking at faster than comfortable velocity[11,20,32,39]. Some improvements in propulsion were retained at 3 months follow-up[20,42], whereas other propulsion measures returned to baseline levels[20,42] (see Table 1). One of these studies compared the effect of electrical stimulation of the ankle dorsiflexors with usual care, and this study did not show superior gains in paretic propulsion with FES[42].

In agreement with the results for propulsion measures, ankle kinetics improved following multiple training sessions with FES delivered to the peroneal nerve[42]. In contrast, no gains in ankle kinetics were observed in one study after a single session with FES delivered to both ankle dorsiflexors and plantarflexors during walking at a comfortable velocity[38]. Four studies reported an increase in walking velocity after the intervention[11,20,39,42].

Modified constraint-induced movement therapy

Three studies evaluated the modified constraint-induced movement therapy approach to train paretic propulsion in individuals with chronic stroke[23,24,30], one of which focused on propulsion as the primary outcome[30]. Two randomized controlled trials concerned a single session[23,24], and one study concerned multiple training sessions[30]. Three weeks of constraint-induced movement therapy using a 'dummy prosthesis' (a below-knee prosthesis to simulate amputee gait, holding the leg in a 90° flexed knee position) at the non-paretic side showed superior gains in paretic propulsion when compared to regular treadmill training[30]. In contrast, immediately after a single session of modified constraint-induced gait training with a mass attached[23] or a robotic constraint applied to the non-paretic leg[24] no changes in paretic propulsion were observed compared to pre intervention[23,24]. At 20 minutes follow-up, paretic propulsion either remained unchanged[23] or increased relative to pre intervention[24]. Neither of these single-session interventions yielded superior effects compared to unconstrained overground or treadmill training[23,24]. The effect of the interventions on walking velocity were ambiguous, with the post-intervention walking velocity being unchanged[23] or increased[24].

Gait training with robotics

Three studies investigated the effect of multiple sessions of robot-assisted gait interventions on propulsion measures[29,46] or ankle kinetics[28] in the chronic phase after stroke. Two studies were randomized controlled trials[29,46], one of which included a propulsion measure as the primary outcome[29]. The interventions concerned a treadmill-integrated ankle robotics training[29], overground gait training with a robot-assisted ankle-foot orthosis[46] or robot-assisted gait training with an endpoint robot system[28].

Treadmill-integrated ankle robotics training improved propulsion measures post intervention, with the gains in propulsion being retained at six weeks follow-up[29]. These gains in the experimental group were superior to those in the control group, who received seated ankle robotics training[29]. In contrast, gait training with a robot-assisted ankle-foot orthosis did not yield improvements in propulsion measures post intervention[46]. These findings were similar to walking with a conventional ankle-foot orthosis[46]. One study evaluated ankle kinetics following robot-assisted gait training with an endpoint robot system and showed improvements in peak ankle power[28]. Walking velocity increased in all experimental groups and remained unchanged in the control groups[28,29,46].

Other exercise interventions

The remaining six studies examined the effect of other types of exercise interventions on ankle kinetics, including movement training with feedback[31,37], strength and conditioning training[36,43], balance training[45] and training with the use of technology[40]. None of these studies evaluated propulsion measures. All studies concerned multiple training sessions, of which five studies were randomized controlled trials[31,36,37,40,45]. Five studies were performed in the chronic phase[31,36,37,43,45] and one study was performed in the subacute phase after stroke[40].

Table 2. Quality assessment of exercise and other interventions according to the Downs and Black scale. Each item was scored 0 to 1 point, except for item 5 (score 0 to 2 points), resulting in a maximum score of 28 points. Study quality is considered to be high if the total score was 19 points or more. Studies that included a propulsion measure as the primary outcome are shown in bold.

	Type of intervention	Study	Reporting										External validity			Internal validity – Bias							Internal validity – confounding						Power	
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Total
Exercise	Treadmill gait training	Mao et al 2015 [35]	1	1	1	1	1	1	1	0	0	1	0	0	1	0	1	1	1	0	1	1	1	1	1	0	1	1	0	19
		Bonnyaud et al 2013 [22]	1	1	1	1	1	1	1	0	0	1	0	0	1	0	0	1	1	1	1	1	1	1	1	0	0	0	0	17
		Combs et al 2012 [27]	1	1	1	1	0	1	1	0	0	1	0	0	1	0	0	1	1	1	1	1	0	0	0	0	0	0	0	13
		Routson et al 2013 [41]	1	1	1	1	0	1	1	0	1	1	0	0	1	0	0	1	1	1	0	1	0	0	0	0	0	1	0	14
		Lewek et al 2018 [34]	1	1	1	1	0	1	1	0	1	1	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	14
		Betschart et al 2018 [21]	1	1	1	1	0	1	1	0	1	1	0	0	1	0	0	1	1	1	1	1	0	0	0	0	0	1	0	15
		Lauziere et al 2014 [33]	0	1	1	1	0	0	0	0	0	1	0	0	0	0	0	1	1	1	0	1	0	0	0	0	0	0	0	8
	Gait training with functional electrical stimulation	Sheffler et al 2015 [42]	0	1	1	1	2	1	1	0	0	1	0	0	0	0	0	1	1	1	0	1	1	1	1	0	1	1	1	18
		Awad et al 2014 [20]	1	1	1	1	0	1	1	1	0	1	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	0	13
		Hsiao et al 2016 [11]	0	1	1	1	0	1	1	0	0	0	0	0	0	0	0	1	1	1	0	1	0	0	0	0	0	1	0	10
		Reisman et al 2013 [39]	1	1	1	1	0	1	1	0	0	0	0	0	0	0	1	1	1	0	1	1	0	0	0	0	0	0	0	11
		Kesar et al 2015 [32]	1	1	1	1	0	1	1	0	1	1	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	14
		Palmer et al 2017 [38]	1	1	1	1	1	1	1	0	1	1	0	0	0	0	0	1	1	1	1	1	1	1	1	0	1	0	0	18
	Gait training according to modified constraint induced movement therapy	Bonnyaud et al 2013 [23]	0	1	0	1	0	1	1	0	0	1	0	0	1	0	0	1	1	1	1	1	1	1	1	0	0	0	0	14
		Bonnyaud et al 2014 [24]	1	1	1	1	1	1	1	0	0	1	0	0	0	0	0	1	1	1	1	1	1	1	1	0	1	0	0	17
		Hase et al 2011 [30]	0	1	1	1	1	1	1	0	1	1	0	0	0	0	0	1	1	0	1	1	0	0	0	0	1	1	1	15
	Gait training with robotics	**Forrester et al 2016 [29]**	1	1	1	1	1	1	0	1	0	1	0	0	0	0	0	1	1	1	1	1	1	1	1	0	1	0	0	17
		Yeung et al 2018 [46]	1	1	1	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	0	1	1	1	1	0	1	1	0	19
		De Luca et al 2018 [28]	1	1	1	1	0	1	1	0	1	1	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	14
	Movement training with feedback	Mirelman et al 2010 [37]	1	0	1	1	1	1	1	1	1	1	0	0	0	1	0	0	1	1	1	1	1	1	1	0	1	1	0	19
		Jonsdottir et al 2010 [31]	1	1	1	1	1	1	1	0	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	0	0	1	0	19
	Strength and conditioning training	Milot et al 2013 [36]	1	1	1	1	1	1	1	0	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	0	1	0	0	19
		Teixeira-Salmela et al 2001 [43]	1	0	1	1	1	1	1	0	1	0	0	0	1	0	0	1	1	1	1	1	0	0	0	0	0	1	0	14
	Balance training	Yavuzer et al 2006 [45]	0	1	1	1	1	1	0	0	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	0	1	1	0	18
	Training with technology	Richards et al 2004 [40]	0	1	1	1	2	1	1	0	1	0	0	0	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	21
Other	Surgical elongation or transfer of the calf muscle-tendon complex	Carda et al 2009 [25]	1	1	1	1	0	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	15
		Carda et al 2010 [26]	0	1	1	1	1	1	1	1	1	1	0	0	0	0	0	1	1	0	1	1	0	1	0	0	1	1	0	16
	Transcranial direct current stimulation	Van Asseldonk & Boonstra 2016 [44]	0	1	1	1	1	0	0	0	1	1	0	0	0	1	1	1	1	1	0	1	1	1	1	0	1	1	0	17

Gains in ankle kinetics were observed after movement training with the use of feedback. Biofeedback provided during overground walking improved ankle kinetics, while the control group receiving usual care did not show changes in ankle kinetics[31]. The use of virtual reality during seated ankle movement training showed superior gains in ankle kinetics compared to the training without virtual reality when patients walked barefooted, but outcomes were similar for the virtual reality and non-virtual reality group when walking with shoes[37]. In a study that combined conventional rehabilitation with the use of technology (i.e. treadmill, limb load monitor or dynamometer) in individuals in the subacute phase after stroke, gains in ankle kinetics over time were not different between training with and without the use of technology[40]. Ankle kinetics remained unchanged at posttest after multiple sessions of strength training, with[43] or without[36] concurrent conditioning training, or balance training[45]. Walking velocity increased in five studies[31,36,37,40,43], and remained constant in one study[45].

Other interventions

Three studies evaluated interventions that did not involve physical exercises, none of which included a propulsion measure as primary outcome. Two studies evaluated the effect of surgical elongation or transfer of the calf muscle-tendon complex on propulsion and ankle kinetics in chronic stroke survivors with equinovarus foot deformity[25,26]. One year after the surgery, propulsion measures improved[25,26] and the gain in propulsion was similar across different surgical procedures (i.e. plantarflexor lengthening and/or tendon transfers[26]). Unlike the observed improvement in propulsion measures, ankle kinetics declined one year after surgery[25]. Both studies showed gains in walking velocity one year after surgery[25,26].

The remaining study examined the effect of transcranial direct current stimulation on walking in chronic stroke survivors[44]. A single session of transcranial direct current stimulation did not affect propulsion measures immediately after the intervention or at 45 minutes follow-up[44]. In addition, results of the stimulation groups were not superior to the sham control condition[44].

Discussion

In the past decade, the field of stroke rehabilitation has gained an interest in interventions for improving the use of the propulsive capacity of the paretic leg. This review aimed to provide an overview of the potential effectiveness of these interventions. The included studies mostly applied exercise interventions (N = 25), whereas a minority of studies focused on surgical interventions (N = 2) or non-invasive brain stimulation (N = 1). Of the total number of 28 studies included in this review, the number of high-quality trials was limited (N = 6). In addition, a wide variety of propulsion measures were reported across studies, with propulsion being the primary outcome measure in eight studies[11,20,27,29,30,32,34,39]. In general, mixed results were reported for interventions that evaluated propulsion measures, with some interventions yielding improvements in propulsion[11,20,25,26,28-34,37,39,42], whereas others did not[21-24,27,35,36,38,40,41,43-46]. Similar results were found for interventions that evaluated ankle kinetics, with some interventions showing increased ankle kinetics[28,31,33,37,42], whereas others did not[21,25,35,36,38,40,43,45].

Mixed results were reported for interventions that involved gait training on a treadmill. The studies that applied regular treadmill training combined with body weight support did not yield any significant improvements in propulsion[27,41]. This may be due to the body weight support reducing the limb loading and, consequently, reducing the ability to generate push-off force. In contrast, the two studies that applied a single session of treadmill training without body weight support all showed gains in propulsion[22,34] with the more convincing effects being demonstrated following treadmill training with an impeding force applied to the pelvis[34]. The study that applied the backward-oriented impeding force during treadmill walking, which manipulation challenges propulsion similar to walking uphill, observed these gains after only three minutes of walking in the experimental condition[34]. Apparently, the effects of this manipulation easily transfer to unrestrained treadmill walking, but the duration of the effects and the transfer to overground walking still need to be determined.

Interventions that combined gait training with functional electrical stimulation of the lower-leg muscles generally showed beneficial effects on paretic propulsion in the vast majority of the studies[11,20,32,39,42]. These effects were observed immediately following a single training session[32] and after a 12-week intervention[11,20,39,42]. Moreover, the improvements in paretic propulsion after the 12-week intervention were retained for at least three months[20,42]. The included functional electrical stimulation interventions varied with regard to which lower-leg muscles were stimulated. The gains in paretic propulsion following gait training combined with electrical stimulation of the peroneal nerve[42] may be explained by the absence of any orthotics worn during training. This may have allowed participants to use their available residual ankle plantarflexion capacity, while not being hindered by an ankle-foot orthosis during push-off[47,48]. Similar beneficial effects on paretic propulsion were reported in four studies that applied stimulation of both ankle dorsal- and plantarflexion muscles, but these studies also involved gait training at faster than comfortable velocities[11,20,32,39]. These studies did not separately report the effects of gait training at fast velocity alone, whereas walking at faster velocities is also known to challenge the propulsive capacity[49]. It thus remains to be determined to what extent the gains in paretic propulsion can in fact be attributed to the applied electrical stimulation or to the faster walking speed.

Interventions based on the principles of constraint-induced movement therapy[50] showed ambiguous effects on paretic propulsion[23,24,30]. Three weeks of treadmill training with a constraint that annihilated propulsion of the non-paretic leg yielded improvements in paretic propulsion post intervention[30], whereas two other studies that applied a single session of walking with a less severe constraint failed to demonstrate such effects[23,24]. These findings are in accordance with those from upper extremity constraint-induced movement therapy that also demonstrate the need for applying stringent constraints to the non-paretic side over a longer time period[51]. Likewise, gait training based on modified constraint-induced movement therapy may only be effective if the constraint sufficiently limits the non-paretic contribution and thus forces the paretic leg to generate greater propulsion during multiple training sessions.

Results of gait training with robotics indicate that assisted walking may be effective for promoting paretic propulsion. Gradual reduction of robotic assistance during walking improved paretic propulsion[29], and ankle kinetics as well[28], during unassisted walking post intervention, with gains in propulsion being retained at six weeks follow-up[29]. In contrast, seated ankle movement training performed with the same device did not improve paretic propulsion, which observation emphasizes the relevance of task-specific training involving walking exercises[29]. Yet, another study on gait training with a robot-assisted ankle-foot orthosis that supported dorsiflexion movements during the swing phase failed to show gains in paretic propulsion[46]. It is, however, unclear from this paper whether the robotic device allowed ankle plantarflexion movements and, thus, propulsion generation during push-off. Hence, the optimal design and potential utility of robotic devices for improving paretic propulsion constitute an area for further research.

Several other studies involving exercise interventions only evaluated ankle kinetics instead of propulsion measures, and the findings should thus be interpreted with caution. Split-belt walking showed gains in ankle kinetics following a single session of walking with the paretic leg on the slow belt[33], but not following repeated training sessions with the leg with the longest step length on the slow belt (which was the paretic leg in eight out of the 12 participants[21]). Yet, it is interesting to note that the leg that had walked on the fast belt (and thus had to work harder during training) showed a significant increase in ankle plantarflexion moment at the follow-up assessment (four weeks after the end of the training[21]). When considering split-belt gait training as an intervention for improving propulsion, these findings raise the question whether the paretic leg should walk on the *fast* belt to challenge propulsion *during* the split walking condition, or on the slow belt to achieve de-adaptation *after-effects* in propulsion, which is an interesting topic for further research. Other types of exercise interventions did not yield improvements in ankle kinetics[35,36,38,40,43,45], except for two exercise interventions combined with the use of (bio)feedback that showed modest effects[31,37]. The suggested working mechanism of these interventions is based on immediate, external feedback about motor performance of the ankle joint supplementing the defective task-intrinsic feedback in patients who suffer from sensory impairments[52]. As sensory disruptions are believed to be common after stroke[53], providing online external feedback on ankle movement may be a valuable adjunct to gait training interventions, but its effect on propulsion measures has yet to be determined.

As a non-exercise intervention, surgical elongation or transfer of the calf muscle-tendon complex in patients with equinovarus foot deformity showed promising results for improving paretic propulsion in a specific subgroup of stroke survivors[25,26]. Before surgery, participants were not able to reach a plantigrade position of the foot with full knee extension, which severely limits locomotion. The greater ankle range of motion following surgery allows for better foot placement and weight acceptance, thereby restoring these prerequisites of walking[25,26]. One year after surgery of the equinovarus foot, peak propulsive force and propulsive symmetry improved whereas, paradoxically, a decline in peak ankle moment and power were observed[25,26]. These findings suggest that participants needed lower ankle moments and powers for efficiently generating propulsion. Surgical interventions may thus have the potential for improving paretic propulsion in a specific subgroup of stroke survivors with equinovarus foot deformity.

In contrast to the variable effects of interventions on propulsion outcomes and/or ankle kinetics, the vast majority of studies showed beneficial effects on walking velocity[11,20-22,24-29,31,35-37,39-43,46]. Half of the studies that demonstrated improved walking velocity did so without concurrent changes in propulsion or ankle kinetics, which suggests that the increased velocity was achieved through the development or strengthening of compensatory mechanisms to overcome deficient paretic push-off. Yet, in some studies, concurrent improvements in walking velocity and propulsion were observed, which point at the use of latent, residual propulsive capacity. The residual propulsive capacity may have become latent due to so-called 'learned non-use' after stroke. By reducing learned non-use, interventions may have elicited such latent propulsive capacity. Indeed, a recently published narrative review by Roelker et al[54] suggests that a minimal degree of ankle plantarflexion function on the paretic side may be necessary to benefit from interventions targeting paretic propulsion. Another interesting question is to what extent motor relearning may be hindered by existing compensatory mechanisms[55]. Future research should therefore examine how to identify those patients who possess residual propulsive capacity and determine whether these patients are indeed likely to respond to interventions for improving paretic propulsion. The results from these future studies may provide a potential avenue for more personalized rehabilitation treatment after stroke.

This review has some limitations. First, the evidence base for propulsion interventions is limited due to a small number of randomized controlled trials, relatively low study quality, and a limited follow-up period of the included studies. Therefore, it was not possible to perform a meta-analysis. Consequently, the notion that interventions challenging and/or enabling the utilization of latent propulsive capacity of the paretic leg may improve paretic propulsion should be interpreted with caution. The same applies to the possible beneficial effects of surgical elongation or transfer of the calf muscle-tendon complex for paretic propulsion in stroke survivors with equinovarus foot deformity. Second, the wide variety of outcome measures made it difficult to compare the effectiveness of interventions. On the other hand, however, the inclusion of multiple propulsion measures made it possible to provide a comprehensive overview of the current evidence for interventions that may improve paretic propulsion. Third, the number of training sessions varied between interventions, which may have influenced the study results. Yet, no a-priori restrictions regarding the minimal number of training sessions were applied to ensure that emerging interventions for improving paretic propulsion were not missed. Fourth, the generalizability of the outcomes is limited, because most interventions were conducted in the chronic phase post stroke. The question remains whether current interventions could also be effective for improving propulsion in the subacute phase after stroke. As most rehabilitation interventions take place in the subacute phase, future research should address this issue.

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References

1. Bohannon RW, Andrews AW, Smith MB. Rehabilitation goals of patients with hemiplegia. Int J Rehabil Res. 1988;11(2):181-184.
2. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1995;76(1):27-32.
3. Olney SJ, Richards C. Hemiparetic gait following stroke. Part I: Characteristics. Gait Posture. 1996;4(2):136-148.
4. Chen IC, Cheng PT, Hu AL, et al. Balance evaluation in hemiplegic stroke patients. Chang Gung Med J. 2000;23(6):339-347.
5. Chen G, Patten C, Kothari DH, Zajac FE. Gait differences between individuals with post-stroke hemiparesis and non-disabled controls at matched speeds. Gait Posture. 2005;22(1):51-56.
6. Patterson KK, Parafianowicz I, Danells CJ, et al. Gait asymmetry in community-ambulating stroke survivors. Arch Phys Med Rehabil. 2008;89(2):304-310.
7. Balaban B, Tok F. Gait disturbances in patients with stroke. PM & R. 2014;6(7):635-642.
8. Schmid A, Duncan PW, Studenski S, et al. Improvements in speed-based gait classifications are meaningful. Stroke. 2007;38(7):2096-2100.
9. Campanini I, Merlo A, Damiano B. A method to differentiate the causes of stiff-knee gait in stroke patients. Gait Posture. 2013;38(2):165-169.
10. Balasubramanian CK, Bowden MG, Neptune RR, Kautz SA. Relationship between step length asymmetry and walking performance in subjects with chronic hemiparesis. Arch Phys Med Rehabil. 2007;88(1):43-49.
11. Hsiao HY, Awad LN, Palmer JA, Higginson JS, Binder-Macleod SA. Contribution of Paretic and Nonparetic Limb Peak Propulsive Forces to Changes in Walking Speed in Individuals Poststroke. Neurorehabil Neural Repair. 2016;30(8):743-752.
12. Shumway-Cook A, Woollacott MH. Motor Control: Theory and Practical Applications. Baltimore: Williams & Wilkins; 1995.
13. Peterson CL, Cheng J, Kautz SA, Neptune RR. Leg extension is an important predictor of paretic leg propulsion in hemiparetic walking. Gait Posture. 2010;32(4):451-456.
14. Bowden MG, Balasubramanian CK, Neptune RR, Kautz SA. Anterior-posterior ground reaction forces as a measure of paretic leg contribution in hemiparetic walking. Stroke. 2006;37(3):872-876.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-34.
16. Bernhardt J, Hayward KS, Kwakkel G, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. Int J Stroke. 2017;12(5):444-450.
17. Olney SJ, Griffin MP, Monga TN, McBride ID. Work and power in gait of stroke patients. Arch Phys Med Rehabil. 1991;72(5):309-314.
18. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-384.
19. Willems LM, Vriezekolk JE, Schouffoer AA, et al. Effectiveness of Nonpharmacologic Interventions in Systemic Sclerosis: A Systematic Review. Arthritis Care Res. 2015;67(10):1426-1439.
20. Awad LN, Reisman DS, Kesar TM, Binder-Macleod SA. Targeting Paretic Propulsion to Improve Poststroke Walking Function: A Preliminary Study. Arch Phys Med Rehabil. 2014;95(5):840-848.
21. Betschart M, McFayden BJ, Nadeau S. Lower limb joint moments on the fast belt contribute to a reduction of step length asymmetry over ground after split-belt treadmill training in stroke: A pilot study. Physiother Theory Pract. 2018;36(9):1-11.
22. Bonnyaud C, Pradon D, Zory R, Bensmail D, Vuillerme N, Roche N. Does a single gait training session performed either overground or on a treadmill induce specific short-term effects on gait parameters in patients with hemiparesis? A randomized controlled study. Top Stroke Rehabil. 2013;20(6):509-518.
23. Bonnyaud C, Pradon D, Zory R, et al. Effects of a gait training session combined with a mass on the non-paretic lower limb on locomotion of hemiparetic patients: A randomized controlled clinical trial. Gait Posture. 2013;37(4):627-630.
24. Bonnyaud C, Zory R, Boudarham J, Pradon D, Bensmail D, Roche N. Effect of a robotic restraint gait training versus robotic conventional gait training on gait parameters in stroke patients. Exp Brain Res. 2014;232(1):31-42.
25. Carda S, Bertoni M, Zerbinati P, Rossini M, Magoni L, Molteni F. Gait Changes After Tendon Functional Surgery for Equinovarus Foot in Patients with Stroke Assessment of Temporo-Spatial, Kinetic, and Kinematic Parameters in 177 Patients. Am J Phys Med Rehabil. 2009;88(4):292-301.
26. Carda S, Molteni F, Bertoni M, Zerbinati P, Invernizzi M, Cisari C. Extensor hallucis longus transfer as an alternative to split transfer of the tibialis anterior tendon to correct equinovarus foot in hemiplegic patients without overactivity of tibialis anterior. J Bone Joint Surg Br. 2010;92(9):1262-1266.
27. Combs SA, Dugan EL, Ozimek EN, Curtis AB. Effects of body-weight supported treadmill training on kinetic symmetry in persons with chronic stroke. Clin Biomech. 2012;27(9):887-892.
28. De Luca A, Vernetti H, Capra C, et al. Recovery and compensation after robotic assisted gait training in chronic stroke survivors. Disabil Rehabil Assist Technol. 2019;14(8):826-838.
29. Forrester LW, Roy A, Hafer-Macko C, Krebs HI, Macko RF. Task-specific ankle robotics gait training after stroke: a randomized pilot study. J Neuroeng Rehabil. 2016;13(1):51.
30. Hase K, Suzuki E, Matsumoto M, Fujiwara T, Liu MG. Effects of Therapeutic Gait Training Using a Prosthesis and a Treadmill for Ambulatory Patients With Hemiparesis. Arch Phys Med Rehabil. 2011;92(12):1961-1966.
31. Jonsdottir J, Cattaneo D, Recalcati M, et al. Task-Oriented Biofeedback to Improve Gait in Individuals With Chronic Stroke: Motor Learning Approach. Neurorehabil Neural Repair. 2010;24(5):478-485.
32. Kesar TM, Reisman DS, Higginson JS, Awad LN, Binder-Macleod SA. Changes in Post-Stroke Gait Biomechanics Induced by One Session of Gait Training. Phys Med Rehabil Int. 2015;2(10):1072.
33. Lauziere S, Mieville C, Betschart M, Duclos C, Aissaoui R, Nadeau S. Plantarflexion moment is a contributor to step length after-effect following walking on a split-belt treadmill in individuals with stroke and healthy individuals. J Rehabil Med. 2014;46(9):849-857.
34. Lewek MD, Raiti C, Doty A. The Presence of a Paretic Propulsion Reserve During Gait in Individuals Following Stroke. Neurorehabil Neural Repair. 2018;32(12):1011-1019.
35. Mao YR, Lo WL, Lin Q, et al. The Effect of Body Weight Support Treadmill Training on Gait Recovery, Proximal Lower Limb Motor Pattern, and Balance in Patients with Subacute Stroke. Biomed Res Int. 2015;2015:175719.
36. Milot M-H, Nadeau S, Gravel D, Bourbonnais D. Gait Performance and Lower-Limb Muscle Strength Improved in Both Upper-Limb and Lower-Limb Isokinetic Training Programs in Individuals with Chronic Stroke. ISRN Rehabil. 2013;2013(1):1-10.
37. Mirelman A, Patritti BL, Bonato P, Deutsch JE. Effects of virtual reality training on gait biomechanics of individuals post-stroke. Gait Posture. 2010;31(4):433-437.
38. Palmer JA, Hsiao H, Wright T, Binder-Macleod SA. Single Session of Functional Electrical Stimulation-Assisted Walking Produces Corticomotor Symmetry Changes Related to Changes in Poststroke Walking Mechanics. Phys Ther. 2017;97(5):550-560.
39. Reisman D, Kesar T, Perumal R, et al. Time Course of Functional and Biomechanical Improvements During a Gait Training Intervention in Persons With Chronic Stroke. J Neurol Phys Ther. 2013;37(4):159-165.
40. Richards CL, Malouin F, Bravo G, Dumas F, Wood-Dauphinee S. The role of technology in task-oriented training in persons with subacute stroke: a randomized controlled trial. Neurorehabil Neural Repair.

2004;18(4):199-211.
41. Routson RL, Clark DJ, Bowden MG, Kautz SA, Neptune RR. The influence of locomotor rehabilitation on module quality and post-stroke hemiparetic walking performance. Gait Posture. 2013;38(3):511-517.
42. Sheffler LR, Taylor PN, Bailey SN, et al. Surface peroneal nerve stimulation in lower limb hemiparesis: effect on quantitative gait parameters. Am J Phys Med Rehabil. 2015;94(5):341-357.
43. Teixeira-Salmela LF, Nadeau S, McBride I, Olney SJ. Effects of muscle strengthening and physical conditioning training on temporal, kinematic and kinetic variables during gait in chronic stroke survivors. J Rehabil Med. 2001;33(2):53-60.
44. Van Asseldonk EHF, Boonstra TA. Transcranial Direct Current Stimulation of the Leg Motor Cortex Enhances Coordinated Motor Output During Walking With a Large Inter-Individual Variability. Brain Stimul. 2016;9(2):182-190.
45. Yavuzer G, Eser F, Karakus D, Karaoglan B, Stam HJ. The effects of balance training on gait late after stroke: a randomized controlled trial. Clin Rehabil. 2006;20(11):960-969.
46. Yeung LF, Ockenfeld C, Pang MK, et al. Randomized controlled trial of robot-assisted gait training with dorsiflexion assistance on chronic stroke patients wearing ankle-foot-orthosis. J Neuroeng Rehabil. 2018;15(1):51.
47. Vistamehr A, Kautz SA, Neptune RR. The influence of solid ankle-foot-orthoses on forward propulsion and dynamic balance in healthy adults during walking. Clin Biomech (Bristol, Avon). 2014;29(5):583-589.
48. Berenpas F, Schiemanck S, Beelen A, Nollet F, Weerdesteyn V, Geurts A. Kinematic and kinetic benefits of implantable peroneal nerve stimulation in people with post-stroke drop foot using an ankle-foot orthosis. Restor Neurol Neurosci. 2018;36(4):547-558.
49. Kesar TM, Reisman DS, Perumal R, et al. Combined effects of fast treadmill walking and functional electrical stimulation on post-stroke gait. Gait Posture. 2011;33(2):309-313.
50. Taub E. Somatosensory deafferentation research with monkeys: Implications for rehabilitation medicine. In Behavioral psychology in rehabilitation medicine: Clinical applications. Ince LP ed. New York: Williams & Wilkins; 1980:371–401.
51. Fleet A, Page SJ, MacKay-Lyons M, Boe SG. Modified constraint-induced movement therapy for upper extremity recovery post stroke: what is the evidence? Top Stroke Rehabil. 2014;21(4):319-331.
52. Muratori LM, Lamberg EM, Quinn L, Duff SV. Applying principles of motor learning and control to upper extremity rehabilitation. J Hand Ther. 2013;26(2):94-102.
53. Connell LA, Tyson SF. Measures of sensation in neurological conditions: a systematic review. Clin Rehabil. 2012;26(1):68-80.
54. Roelker SA, Bowden MG, Kautz SA, Neptune RR. Paretic propulsion as a measure of walking performance and functional motor recovery post-stroke: A review. Gait Posture. 2019;68:6-14.
55. Awad LN, Reisman DS, Pohlig RT, Binder-Macleod SA. Identifying candidates for targeted gait rehabilitation after stroke: better prediction through biomechanics-informed characterization. J Neuroeng Rehabil. 2016;13(1):84.

Supplementary files

Appendix 1. Search strategies

Pubmed
(cerebrovascular disorders [mesh] OR paresis [mesh] OR hemiplegia [mesh] OR stroke OR cva OR cerebrovascular) AND (rehabilitation [mesh] OR exercise [mesh] OR therapeutics [mesh] OR intervention OR training OR therapy OR rehabil*) AND (walking [mesh] OR lower extremity [mesh] OR walking OR gait) AND (propulsion OR propulsive OR ground reaction force OR GRF OR (kinetic* AND force))

Web of Science
((cerebrovascular disorde* OR infarc* OR ischem* OR pares* OR hemipares* OR hemiplegi* OR monoplegi* OR stroke OR cva OR cerebrovascular) AND (rehabilitation OR exercis* OR therap* OR intervention OR training OR activit* OR treatment) AND (walk OR walk* OR ambulat* OR gait OR locomotion OR lower extremit* OR lower limb* OR leg) AND (propulsion OR propulsive OR ground reaction force OR GRF OR (kinetic* AND force)))

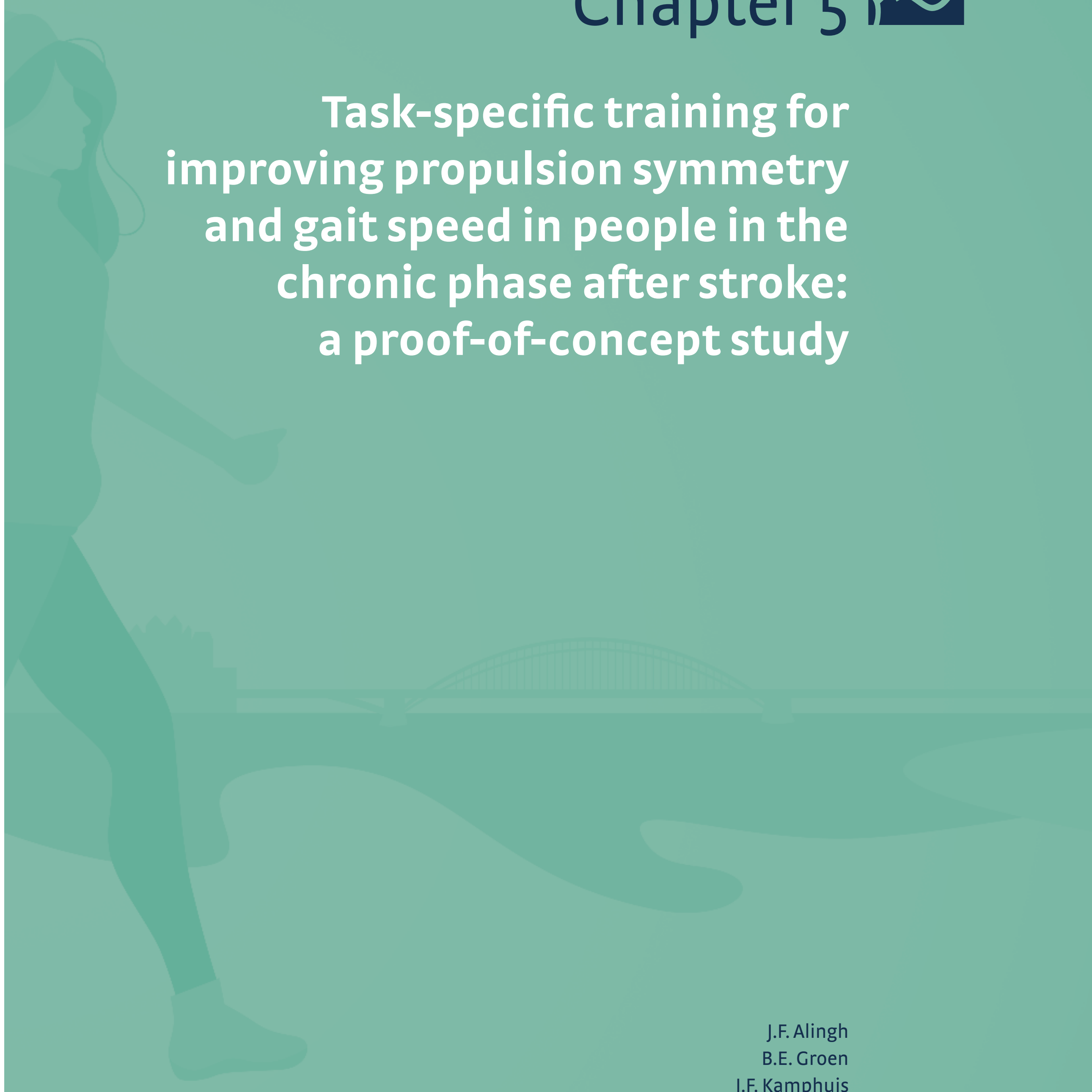
Embase
((cerebrovascular disorder* OR infarct* OR ischemi* OR pares* OR hemipares* OR hemiplegia* OR monoplegia* OR stroke OR cva OR cerebrovascular) AND (rehabilitation OR exercise* OR therap* OR intervention OR training OR activit* OR treatment) AND (walk* OR ambulat* OR gait OR locomotion OR lower extremit* OR lower limb* OR leg) AND (propulsion OR propulsive OR ground reaction force OR GRF OR (kinetic* AND force))).af

PEDro
#1 Abstract & title: Ground reaction force walking; Subdiscipline: neurology
#2 Abstract & title: Ground reaction force gait; Subdiscipline: neurology
#3 Abstract & title: GRF walking; Subdiscipline: neurology
#4 Abstract & title: GRF gait; Subdiscipline: neurology
#5 Abstract & title: kinetic* force walking; Subdiscipline: neurology
#6 Abstract & title: kinetic* force gait; Subdiscipline: neurology
#7 Abstract & title: propuls* walking; Subdiscipline: neurology
#8 Abstract & title: propuls* gait; Subdiscipline: neurology

Appendix 2. Downs and Black scale

Questions	Score		Explanation
Reporting			
1. Is the hypothesis/ aim/objective of the study clearly described?	YES	1	Studies must report on what outcome dimension(s) the intervention aims to be effective.
	NO	0	
2. Are the (main) outcomes to be measured clearly described in the Introduction or Methods section?	YES	1	If the main outcomes are first mentioned in the Results section, the question should be answered NO.
	NO	0	
3. Are the characteristics of the patients included in the study clearly described?	YES	1	In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.
	NO	0	
4. Are the interventions of interest clearly described?	YES	1	Treatments and placebo (where relevant) that are to be compared should be clearly described (including duration and frequency).
	NO	0	
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	YES	2	A list of principal confounders is provided. In the Methods section it must be explicitly mentioned that confounders were taken into account. When baseline comparison between groups are present, this should be answered Partially. Studies with a single group design should be answered NO.
	Partially	1	
	NO	0	
6. Are the (main) findings of the study clearly described?	YES	1	Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions (This question does not cover statistical tests which are considered below).
	NO	0	
7. Does the study provide estimates of the random variability in the data for the main outcomes?	YES	1	In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes. If not applicable, this should be answered NO.
	NO	0	
8. Have all important adverse events that may be a consequence of the intervention been reported?	YES	1	In the Methods or Results section it must be mentioned that adverse events were assessed.
	NO	0	
9. Have the characteristics of patients lost to follow-up been described?	YES	1	This should be answered YES where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion (< 20% lost to follow-up). This should be answered NO where a study does not report the number of patients lost to follow-up.
	NO	0	
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the (main) outcomes except where the probability value is less than 0.001?	YES	1	In table or text.
	NO	0	
External validity All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.			
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	YES	1	The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived the question should be answered as Unable to determine.
	NO	0	
	Unable to determine	0	
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	YES	1	The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.
	NO	0	
	Unable to determine	0	
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	YES	1	The question should be answered NO if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.
	NO	0	
	Unable to determine	0	
Internal validity- bias			
14. Was an attempt made to blind study subjects to the intervention they have received?	YES	1	For studies where the patients would have no way of knowing which intervention they received, this should be answered YES.
	NO	0	
	Unable to determine	0	
15. Was an attempt made to blind those measuring the (main) outcomes of the intervention?	YES	1	
	NO	0	
	Unable to determine	0	
16. If any of the results of the study were based on "data dredging", was this made clear?	YES	1	Any outcome analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer YES.
	NO	0	
	Unable to determine	0	
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?			
	YES	1	Where follow-up was the same for all study patients the answer should be YES. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be YES. Studies where differences in follow-up are ignored should be answered NO.
	NO	0	
	Unable to determine	0	
18. Were the statistical tests used to assess the (main) outcomes appropriate?	YES	1	The statistical techniques used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there was no evidence of bias, the question should be answered YES. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered YES.
	NO	0	
	Unable to determine	0	
19. Was compliance with the intervention/s reliable?	YES	1	Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered NO. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered YES.
	NO	0	
	Unable to determine	0	
20. Were the (main) outcome measures used accurate (valid and reliable)?	YES	1	For studies where the outcome measures are clearly described, the question should be answered YES. For studies which refer to other work or that demonstrates the outcome measures are accurate or widely accepted in rehabilitation after stroke, the question should be answered YES.
	NO	0	
	Unable to determine	0	
Internal validity- confounding (selection bias)			
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	YES	1	For example, patients for all comparison groups should be selected from the same hospital. The question should be answered Unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.
	NO	0	
	Unable to determine	0	

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	YES	1	For the study which does not specify the time period over which patients were recruited, the question should be answered as Unable to determine.
	NO	0	
	Unable to determine	0	
23. Were study subjects randomised to intervention groups?	YES	1	Studies which state that subjects were randomised should be answered YES except where method of randomisation would not ensure random allocation. For example alternate allocation would score NO because it is predictable.
	NO	0	
	Unable to determine	0	
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	YES	1	All non-randomised studies should be answered NO. If assignment was concealed from patients but not from staff, it should be answered NO.
	NO	0	
	Unable to determine	0	
25. Was there adequate adjustment for confounding in the analyses from which the (main) findings were drawn?	YES	1	This question should be answered NO for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of know confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered NO.
	NO	0	
	Unable to determine	0	
26. Were losses of patients to follow-up taken into account?	YES	1	If the numbers of patients lost to follow-up are not reported, the question should be answered as Unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered YES (< 20% lost to follow-up).
	NO	0	
	Unable to determine	0	
Power			
27. Did the study included a power analysis or reported minimal clinically important difference effects?	YES	1	When a power analysis is conducted this question should be answered YES.
	NO	0	



Chapter 5

Task-specific training for improving propulsion symmetry and gait speed in people in the chronic phase after stroke: a proof-of-concept study

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Abstract

Background
After stroke, some individuals have latent, propulsive capacity of the paretic leg, that can be elicited during task-specific gait training. The aim of this proof-of-concept study was to investigate the effect of five-week robotic gait training for improving propulsion symmetry by increasing paretic propulsion in chronic stroke survivors.

Methods
Twenty-nine individuals with chronic stroke and impaired paretic propulsion (≥8% difference in paretic vs. non-paretic propulsive impulse) were enrolled. Participants received ten 60-min sessions of individual robotic gait training targeting paretic propulsion (five weeks, twice a week), complemented with home exercises (15 min/day) focusing on increasing strength and practicing learned strategies in daily life. Propulsion measures, gait kinematics and kinetics, self-selected gait speed, performance of functional gait tasks, and daily-life mobility and physical activity were assessed five weeks (T0) and one week (T1) before the start of intervention, and one week (T2) and five weeks (T3) after the intervention period.

Results
Between T0 and T1, no significant differences in outcomes were observed, except for a marginal increase in gait speed (+2.9%). Following the intervention, propulsion symmetry (+7.9%) and paretic propulsive impulse had significantly improved (+8.1%), whereas non-paretic propulsive impulse remained unchanged. Larger gains in propulsion symmetry were associated with more asymmetrical propulsion at T0. In addition, following the intervention significantly greater paretic trailing limb angles (+6.6%) and ankle plantarflexion moments (+7.1%) were observed. Furthermore, gait speed (+7.2%), 6-Minute Walk Test (+6.4%), Functional Gait Assessment (+6.5%), and daily-life walking intensity (+6.9%) had increased following the intervention. At five-week follow-up (T3), gains in all outcomes were retained, and gait speed had further increased (+3.6%).

Conclusions
The post-intervention gain in paretic propulsion did not only translate into improved propulsion symmetry and gait speed, but also pertained to performance of functional gait tasks and daily-life walking activity levels. These findings suggest that well-selected chronic stroke survivors may benefit from task-specific targeted training to utilize the residual propulsive capacity of the paretic leg. Future research is recommended to establish simple baseline measures for identification of individuals who may benefit from such training and confirm benefits of the used training concepts in a randomized controlled trial.

Trial registration: ClinicalTrials.gov (www.clinicaltrials.gov): NCT04650802. Retrospectively registered 3 December 2020.

Introduction

While the majority of stroke survivors regain independent walking[1], gait efficiency and speed are often persistently reduced compared to healthy adults[2]. Post-stroke gait speed is associated with community ambulation, as a minimum speed of 0.4 m/s seems necessary for walking outside the home, and a speed faster than 0.8 m/s seems required for full community ambulation[3,4]. In addition, impaired post-stroke gait speed is associated with reduced quality of life[5,6]. Hence, a common goal for post-stroke rehabilitation interventions is to improve gait speed.

Gait speed is mainly generated by ankle push-off force during terminal stance, which helps propel the body forward. Gait propulsion is usually defined as the horizontal component of the ground reaction force during push-off. Propulsion is determined by the ankle plantarflexion moment[7], in combination with the angle of the trailing limb with the vertical during push-off[8-10]. Generally, larger trailing limb angles are associated with more anteriorly directed ground reaction forces[11], resulting in a larger contribution of the ankle plantarflexion moment to forward (instead of upward) acceleration of the body. After stroke, propulsion of the paretic leg is often lower than the values observed in healthy adults[12-14]. This is probably due to muscle weakness[9,15,16], loss of selective motor control[17], and/or balance uncertainty and reduced limb loading[18]. Reductions in paretic compared to non-paretic propulsion result in propulsion asymmetry[19], which is associated with impaired walking capacity1[9-21]. In addition, deficits in paretic propulsion are associated with reduced paretic knee flexion during swing[22,23], which may affect walking efficiency[24,25] and increase the risk of falling[26]. In order to compensate for the lack of paretic propulsion, stroke survivors tend to rely more on the non-paretic leg's propulsion generation[19,27], as well as on paretic hip pull-off to progress the paretic leg during swing[14,16]. These compensatory mechanism are, however, associated with reduced gait efficiency[25,28]. Increasing the contribution of the paretic leg to propulsion is, therefore, a key target for restoring gait post stroke[29].

A recent review of studies evaluating propulsion and gait speed after single or multiple training sessions suggested that individuals in the chronic phase after stroke may not fully utilize their residual propulsive capacity, possibly due to 'learned non-use' of the paretic leg[30]. It was suggested that targeted and challenging training focusing on stronger ankle plantarflexion and larger trailing limb angle may help people with stroke reactivate this latent propulsive capacity of the paretic leg, thus improving propulsion symmetry[21,30,31]. Yet, to date only few studies involved training programs primarily aimed at improving propulsion in individuals in the chronic phase after stroke[32-37], of which some evaluated the long-term training effects[32-34]. Overall, these studies yielded mixed results[32-37]. Their findings suggest that the latent propulsive capacity of the paretic leg can be elicited during task-specific training in individuals with chronic stroke, but it remains questionable if benefits are retained over time.

The primary aim of this study was to investigate the effect of a five-week gait training for improving propulsion symmetry by increasing propulsion of the paretic leg in individuals in the chronic phase after stroke. The training was conducted in robotic gait trainer LOPES II[38]. LOPES II training allowed participants to focus attention on their paretic leg, attributable to the provided balance support and guided weight shifts. Compensatory movements could be reduced through mechanical assistance of the lower limbs (by LOPES II) and by providing real-time feedback of the individual's gait performance. Propulsion was challenged by increasing step length and velocity, or moving against robotic resistance. In addition to paretic leg propulsion, we also determined its constituent factors, namely the trailing limb angle and the ankle plantarflexion moment of the paretic leg. Our secondary aim was to determine whether the capacity of participants to increase their paretic propulsive impulse at baseline would be an indicator of the latent propulsive capacity of the paretic leg[39] and, thus, a relevant patient-related predictor of a positive training response. In addition, we assessed paretic knee flexion during swing (ICF-impairment level); self-selected gait speed and functional gait tasks (ICF-capacity level); and daily-life mobility impact and physical activity (ICF-performance level). We hypothesized that five weeks (ten sessions) of gait training in LOPES II would improve propulsion symmetry and, thereby, gait speed and execution of functional gait tasks. In addition, we expected that improved gait capacity might lead to a lower impact of stroke on daily-life mobility and a higher physical activity level.

Methods

Participants

Individuals in the chronic phase after stroke were recruited between December 2018 and December 2019 from the outpatient departments of the Radboud University Medical Center and the Sint Maartenskliniek (Nijmegen, the Netherlands). Inclusion criteria were: 1) adult age (≥ 18 years), 2) unilateral, ischemic or hemorrhagic, supratentorial stroke longer than 6 months post onset, 3) impaired propulsion of the paretic leg during walking at self-selected speed (i.e. ≥ 8% difference in paretic vs non-paretic propulsive impulse), 4) capacity to walk 10 meter without support or use of a walking aid (Functional Ambulatory Categories[40]/FAC 3-5), and 5) capacity to walk for five consecutive minutes, with or without the use of a walking aid. Exclusion criteria were: 1) inability to move the body upward against gravity while standing on both legs (loss of calf muscle strength assessed with the Medical Research Council[41]/MRC scale < 3), 2) severe cognitive problems assessed with the Mini-Mental State Examination[42] (MMSE < 24), 3) depressed mood assessed with the Hospital Anxiety and Depression Score[43] (HADS > 7), 4) persistent unilateral visuospatial neglect assessed with the Star Cancellation Test[44] (score < 44), 5) any medical condition interfering with gait, 6) inability to understand verbal instructions, or 7) inappropriate or unsafe fitting of the robotic gait trainer, due to severe lower limb spasticity (Modified Ashworth Scale[45]/MAS ≥ 3), severe lower limb contractures, body weight ≥ 140 kg, or skin problems at body sites where the harness or straps were to be fitted. After inclusion, the following demographic and clinical characteristics were collected: sex, age (years), type of stroke (ischemic/hemorrhagic), time since stroke (months), hemiparetic side, ambulatory capacity (FAC; range 0-5), lower limb motor selectivity (Fugl Meyer Assessement[46] – leg score 0-34), lower limb strength (Motricity Index[47] – leg score 0-100). The study protocol (NL 62617.091.17) was approved by the Medical Ethical Board of the region Arnhem-Nijmegen (the Netherlands). All procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained for all participants.

Study design

We conducted a longitudinal intervention study with two consecutive baseline assessments and a five-week follow-up to determine proof of concept. Assessments were performed five weeks (T0) and one week (T1) before the start of the intervention, and one week (T2) and five weeks (T3) after the end of the five-week intervention period.

Intervention

Each participant received two 60-minute sessions of individual robotic gait training per week, for five weeks, to target paretic propulsion. Robotic gait training was performed using LOPES II, a treadmill based exoskeleton, combined with a body-weight support system (MOOG BV, Nieuw-Vennep, the Netherlands). For a detailed description of the LOPES II see Meuleman et al[38]. All training sessions were delivered by an experienced LOPES II trainer. To help elicit the latent propulsive capacity of the paretic leg, the robotic gait training included three key elements. First, weight shift guidance was applied to the pelvis and levels of body-weight support were set to a minimum, to improve weight acceptance on the paretic leg, necessary for push-off[18]. Second, minimal levels of general guidance force were applied to help participants match their gait pattern with the reference trajectory of the LOPES II, thereby reducing compensatory movements that may limit the need to generate paretic propulsion. If tolerated, the robotic guidance force was gradually reduced over time, while striving for a normal gait pattern. Third, step length and gait speed were increased and, if possible, participants were asked to move against the robotic assistance, to even further challenge the propulsion of the paretic leg. Across training sessions, progressive training intensity was provided by increasing gait speed, reducing assistance and limiting resting breaks. During each training session, participants received real-time feedback of the targeted gait parameter (i.e., weight shift, hip extension, estimated push-off, or step length) by the user interface of the LOPES II, which was projected on a tv-screen in front of the participant. Additionally, participants received verbal feedback from the LOPES II trainer. Training settings were recorded in a logbook. The robotic gait training was complemented with daily, 15-minute home exercises. The home exercises consisted of two parts. The first part contained exercises to bilaterally improve calf muscle strength (e.g. standing heel raises, and forward or backward step-up). The second part consisted of exercises to practice the learned strategies to increase paretic propulsion in daily life (e.g. weight acceptance on the paretic leg in stance and during stepping, and level walking with variable speed or step length). The frequency and duration of the performed home exercises were recorded in a logbook.

5

Outcome measures

At each assessment a 3D-gait analysis and functional gait tasks were performed. In addition, daily-life mobility and physical activity were evaluated. For the 3D-gait analysis, reflective markers (n=39) were attached to the body according to the Plug-In-Gait Full Body model (Plug-In-Gait, Vicon Motion Systems, Ltd, Oxford, UK), and recorded by eight infrared cameras (f_s=100 Hz; Vicon mX 1.7.1, Oxford Metrics, UK). Participants wore their own shoes. Use of a walking aid or ankle-foot orthosis was not allowed. Participants were instructed to walk at their self-selected, comfortable speed along a straight six-meter walkway with two embedded force plates (Kistler, Kistler Group, Winterthur, Switzerland) to record 3D ground reaction force data (f_s= 1000 Hz). At least five strides were collected in which either of both feet hit the respective force plate. During the 3D-gait analysis at T0, participants were also asked to walk along the walkway at a fast speed, during which at least five strides were collected where both feet hit the respective force plates. Functional gait tasks included the 6-Minute Walk Test[48] (6MWT) and the Functional Gait Assessment[49] (FGA; range 0-30). Daily-life mobility and physical activity were assessed with the Stroke Impact Scale[50] (SIS - domain Mobility; range 0-100) and an activity tracker (Activ8, Remedy Distribution Ltd., Valkenswaard, The Netherlands), respectively. The activity tracker Activ8 has been shown to be sufficiently accurate in detecting daily-life physical activity in individuals after stroke[51]. At the end of each assessment, the activity tracker was attached to the non-paretic thigh using waterproof skin tape. The week following each assessment, participants wore the activity tracker for 24 hours a day, for a minimum of five consecutive days.

Data analysis

Custom written software (MATLAB, Mathworks Inc, Natrick, MA, USA) was used to analyze the data of the 3D-gait analysis. Ground reaction force data were filtered with a low-pass, fourth order, bidirectional, Butterworth filter at 10 Hz. The primary outcome was propulsion symmetry at self-selected speed. For each trial, we calculated the propulsive impulse of the paretic and the non-paretic leg as the time integral of the anterior ground reaction force during the stance phase of gait, normalized for the individual's body weight (N/s/kg). Propulsion symmetry was calculated by dividing the paretic propulsive impulse by the sum of the paretic and non-paretic propulsive impulses[19]. Self-selected gait speed (m/s) and paretic leg trailing limb angle[11] (°) were determined for each stride collected during the 3D-gait analysis, using the position data of the C7 marker, and the position of the hip joint center and toe marker, respectively. In addition, Vicon Plug-In-Gait model and software were used to calculate paretic ankle plantarflexion moment (Nm/kg) for each stride. The trailing limb angle and ankle plantarflexion moment of the paretic leg were calculated at the instant of peak paretic anterior ground reaction force. Vicon Plug-In-Gait model and software were also used to determine peak paretic knee flexion during swing. At T0, a 'propulsion capacity score' was determined, which was defined as the difference in paretic propulsive impulse during walking at fast vs. self-selected speed of the gait strides obtained during the 3D-gait analysis. The propulsion capacity score was used to determine the association between baseline capacity to increase paretic propulsive impulse and the training response. Mobility data of the activity trackers was analyzed using Activ8 software. Total time (minutes/day) and intensity (counts/minute) of walking were determined per day, and averaged over the number of days (minimum of five days) that the activity tracker was worn per assessment.

Power calculation

Power analysis performed using STATA version 13 revealed that a sample size of 21 participants (α=0.05; β=0.20) was sufficient to show a difference in propulsion symmetry of 2.73±4.32% (half the intervention effect reported by Awad et al[32]) after the intervention. To determine the association between two relevant patient-related factors and a positive response to training, considering a rule of thumb to include 10-15 participants per predictor and taking into account a drop-out rate of 10%, we aimed for inclusion of 33 participants.

Statistical analysis

Statistical analyses were performed using SPSS statistics version 25 (IBM Statistics, Chicago, USA). Propulsion symmetry, self-selected gait speed, paretic trailing limb angle, and paretic ankle plantarflexion moment were averaged per individual across all strides per assessment (T0-T3). Changes in baseline values between T0 and T1 were determined for each outcome measure using a paired-samples t-test or Wilcoxon Signed Rank Test, depending on data distribution. To assess changes in propulsion symmetry, propulsion impulse of the paretic and non-paretic leg, paretic ankle plantarflexion moment, paretic trailing limb angle, self-selected gait speed, performance on the 6MWT and FGA, and daily-life mobility and physical activity, linear mixed models for repeated measures were fit. The linear mixed models included as fixed effects: 1) the main effect of intervention ('*Intervention* effect', combined score of T0 and T1 vs. combined score of T2 and T3), 2) a covariate 'baseline value' at T0 ('*Baseline*'), 3) an interaction effect of baseline with intervention effect ('*Intervention*Baseline* interaction'), and 4) the effect of follow-up ('*Follow-up* effect', T2 vs. T3). In addition, the effect of intervention on peak paretic knee flexion during swing was analyzed for a subgroup of participants with reduced peak knee flexion at T0 (peak knee flexion ≤ 54°[52]). Since no changes were found between peak paretic knee flexion at T0 and T1 in this subgroup, peak paretic knee flexion at T0 was used as a reference and compared to peak paretic knee flexion at T2, using a Wilcoxon Signed Rank test. Furthermore, to determine whether the propulsion capacity score at T0 was associated with the effect of intervention on propulsion symmetry (T0 vs. T2), a linear mixed model was fit which included as fixed effects: 1) the propulsion capacity score at T0, and 2) a covariate 'propulsion symmetry at T0'. Results of the mixed models were obtained using a restricted maximum likelihood estimation, and an autoregression variance-covariance matrix to account for the correlation between the repeated measures (if applicable). The significance level was set at $p \leq 0.05$ for all tests.

Results

Twenty-nine individuals in the chronic phase after stroke were included in this study. Table 1 provides an overview of the baseline characteristics of the participants. The participants completed a median of 9.1 robotic gait training sessions (range: 7-10 training sessions). In addition, they completed a median of 21 (range: 15-33) sessions of home exercises. Due to technical problems, the 3D-gait analysis at T1 could not be performed in one participant. Moreover, the follow-up assessment (T3) of six participants could not be performed due to lab closure as a result of the COVID-19 pandemic. As such, data of 23 participants was analyzed at T3. No adverse events were reported.

Table 1. Baseline demographic and clinical characteristics (mean ± SD or number) of the participants (N=29)

Sex, male/female (n)	12 / 17
Age (years)	61.0 ± 8.1
Type of stroke, ischemic/hemorrhagic (n)	25 / 4
Time since stroke (months)	21.2 ± 10.7
Hemiparetic side, left/right (n)	15 / 14
FAC (n)	
3	9
4	16
5	4
Self-selected walking speed (m/s)	1.03 ± 0.21
Fugl-Meyer Assessment – leg score (0-34)	23.6 ± 4.9
Motricity index – leg score (0-100)	72.8 ± 9.0%
MRC – calf muscle (n) (0-5)	
3	16
4	8
5	5
MMSE (0-30)	28.2 ± 2.5
HADS – depression (0-21)	2.7 ± 2.4
Star Cancellation Test (0-54)	51.5 ± 2.9

FAC score: Functional Ambulatory Categories; MRC: Medical Research Council scale; MMSE: Mini-Mental State Examination; HADS: Hospital Anxiety and Depression Scale – subscale depression

Propulsion measures

Between T0 and T1, mean propulsion symmetry, and paretic and non-paretic propulsive impulse did not significantly differ ($p \geq 0.114$). Figure 1 shows propulsion symmetry over time. The corresponding test statistics of the mixed models are reported in Supplementary Table S1. Following the intervention, mean propulsion symmetry had significantly improved by 7.9% (see Table 2; *Intervention* effect, $p < 0.001$), whereas it did not differ between post-intervention and follow-up (*Follow-up* effect, $p = 0.083$). Greater improvements in propulsion symmetry were observed in participants with more asymmetric values at baseline (*Intervention*Baseline* interaction, $p < 0.001$). The gain in propulsion symmetry was not associated with the propulsion capacity score at T0 (mean ± SD: 0.03 ± 0.03 N/s/kg; $p = 0.984$).

Following the intervention, the change in propulsion symmetry was accompanied by a significant increase in mean paretic propulsive impulse (8.1%; *Intervention* effect, $p = 0.032$), whereas no significant change of the mean non-paretic propulsive impulse was observed (*Intervention* effect, $p = 0.190$). During follow-up, neither paretic nor non-paretic propulsive impulse showed any change (*Follow-up* effect, $p \geq 0.724$). The gain in paretic propulsive impulse following the intervention was not associated with the paretic propulsive impulse at T0 (*Intervention*Baseline* interaction, $p = 0.183$).

Table 2. Means (± SDs) of propulsion measures, capacity measures, and daily-life mobility and physical activity assessed five weeks before (T0), one week before (T1), immediately after (T2) and five weeks after (T3) the intervention period.

	T0 n = 29	T1 n = 28 [a]	T2 n = 29	T3 n = 23
Propulsion measures				
Propulsive impulse				
Symmetry *†	0.42 ± 0.04	0.42 ± 0.05	0.45 ± 0.05	0.46 ± 0.06
Paretic leg (N/s/kg) *	0.21 ± 0.07	0.22 ± 0.08	0.23 ± 0.07	0.24 ± 0.08
Non-paretic leg (N/s/kg)	0.27 ± 0.06	0.28 ± 0.06	0.26 ± 0.08	0.27 ± 0.08
Trailing limb angle – paretic leg (°) *†	11.7 ± 4.8	12.8 ± 5.1	12.9 ± 4.3	13.3 ± 4.7
Ankle plantarflexion moment – paretic leg (Nm/kg) *†	12.1 ± 3.5	11.8 ± 3.9	12.9 ± 3.8	12.7 ± 3.1
Capacity measures				
Gait speed (m/s) *†‡#	1.04 ± 0.20	1.07 ± 0.22	1.11 ± 0.21	1.15 ± 0.19
6MWT (m) *	429.5 ± 116.7	434.0 ± 117.7	456.3 ± 112.6	463.4 ± 124.5
FGA (0-30) *	19.0 ± 3.0	19.0 ± 2.6	20.3 ± 2.7	20.2 ± 2.7
Daily-life mobility and physical activity				
SIS – Mobility (0-80)	48.8 ± 3.4	49.4 ± 4.0	52.6 ± 4.5	51.7 ± 4.2
Activ8 walking				
Total time (min/day)	112 ± 40	108 ± 41	113 ± 40	115 ± 40
Total intensity (counts/day) *	1198 ± 306	1174 ± 306	1241 ± 286	1300 ± 310

‡ significant difference between T0 and T1, p≤0.05; * significant difference between baseline (combined scores of T0 and T1) and post-intervention (combined scores of T2 and T3), p≤0.05; † significant *Intervention x Baseline* interaction, p≤0.05; # significant difference between T2 and T3, p≤0.05. [a] propulsion measures and gait speed are reported for 28 participants, whereas all other outcomes evaluated at T1 are reported for 29 participants. 6MWT: 6-Minute Walk Test; FGA: Functional Gait Assessment; SIS: Stroke Impact Scale.

The mean trailing limb angle and mean ankle plantarflexion moment of the paretic leg did not differ between T0 and T1 ($p \geq 0.421$). Following the intervention, these variables had significantly increased by 6.6% and 7.1%, respectively (*Intervention* effect, $p \leq 0.002$), but did not change between post-intervention and follow-up (*Follow-up* effect, $p \geq 0.291$). Greater improvements in trailing limb angle and ankle plantarflexion moment were observed in participants with smaller baseline trailing limb angle and ankle plantarflexion moment, respectively (*Intervention*Baseline* interaction, $p \leq 0.008$).

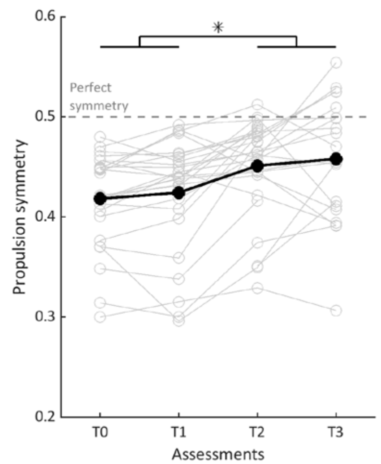

Figure 1. Average group (black line) and individual (grey lines) propulsion symmetry scores across assessments (T0-T3). A value of 0.5 represents perfect symmetry. * significant difference between baseline (combined scores of T0 and T1) and post-intervention (combined scores of T2 and T3), p < 0.05

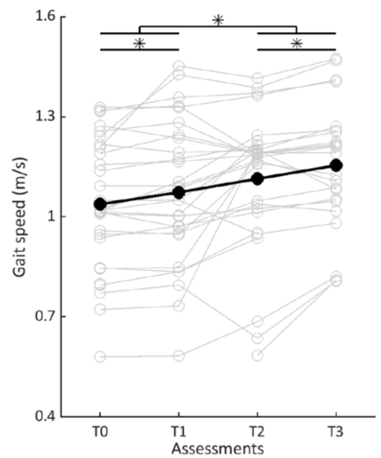

Figure 2. Average group (black line) and individual (grey lines) gait speed across assessments (T0-T3). * significant differences between assessments T0 and T1, between assessments T2 and T3, and between baseline (combined scores of T0 and T1) and post-intervention (combined scores of T2 and T3), p < 0.05

Capacity measures
Mean self-selected gait speed had significantly increased by 2.9% between T0 and T1 ($t(27) = 2.146$, $p = 0.042$), and showed a significant further increase of 7.2% following the intervention (*Intervention* effect, $p < 0.001$), and another 3.6% increase between post-intervention and follow-up (*Follow-up* effect, $p = 0.050$; see Figure 2). Greater increases in gait speed were observed in participants with a slower gait speed at baseline (*Intervention*Baseline* interaction, $p < 0.001$). Mean scores on the 6MWT and FGA did not significantly differ between T0 and T1 ($p \geq 0.327$), significantly improved following the intervention by 6.4% and 6.5%, respectively (*Intervention* effect, $p < 0.019$), but did not change between post-intervention and follow-up (*Follow-up* effect, $p \geq 0.175$). The gain in performance on the 6MWT and FGA was not associated with baseline scores at T0 (*Intervention*Baseline* interaction, $p \geq 0.148$).

Daily-life mobility and physical activity
Mean scores on the SIS-Mobility and the mean total walking time per day did not significantly differ between T0 and T1 ($p \geq 0.202$), nor following the intervention (*Intervention* effect, $p \geq 0.108$), or during follow-up (*Follow-up* effect, $p \geq 0.122$). The total intensity of walking did not differ between T0 and T1 ($p = 0.248$), significantly increased by 6.9% following the intervention (*Intervention* effect, $p = 0.003$), but did not change during follow-up (*Follow-up* effect, $p = 0.496$). The increase in total intensity of walking following the intervention was not associated with the intensity of walking at T0 (*Intervention*Baseline interaction*, $p = 0.056$).

Knee flexion during swing
For participants with reduced peak paretic knee flexion during swing at T0 (N=9, mean ± SD: 36.4 ± 13.9°), peak paretic knee flexion during swing had increased at T2 (mean ± SD: 46.4 ± 12.4°), which difference bordered significance ($p = 0.051$). Peak knee flexion data at T3 were only available for seven participants (mean ± SD: 46.5 ± 16.5°). This sub-group was considered too small to allow further statistical analysis.

Discussion

Individuals in the chronic phase after stroke received five weeks of training targeting propulsion generation during gait. In line with our hypothesis, we found that propulsion symmetry had improved following the intervention, which improvement could be attributed to a larger contribution of the paretic leg. Propulsion generated by the non-paretic leg remained constant over time. The increase in paretic propulsion was observed in parallel with greater paretic ankle plantarflexion moments as well as larger paretic trailing limb angles. Individuals with more asymmetrical propulsion at baseline showed larger gains in propulsion symmetry following the intervention, whereas the ability to increase paretic propulsion during walking at a faster speed at baseline (propulsion capacity score) was not correlated with the intervention effect. Following the intervention, self-selected gait speed, performance on the 6-Minute Walk Test and the Functional Gait Assessment, and the intensity of walking in daily life had also increased. At five-week follow-up, the gains in all of these outcome measures were retained.

Our findings strongly support the emerging notion that in the chronic phase after stroke, paretic propulsion can be improved by targeted interventions[30]. The observation that paretic propulsion and gait speed improved concurrently is in line with previous studies[32,34,36,37,53]. Our results also confirmed previous reports of retention of these concurrent improvements during follow-up periods from six weeks to six months[32,34,53]. Notably, our results were obtained after only 10 task-specific training sessions in five weeks, whereas previous task-specific training included six to 12-weeks of training, three times a week[32,34,36,37,53]. As propulsion is a key determinant of gait speed, it is likely that the increase in gait speed can be attributed to improvements in propulsion. Contradictory to our findings, some previous studies reported gains in gait speed without changes in paretic propulsion following gait interventions[33,54,55]. An increase in gait speed in the absence of improvements in paretic propulsion points at the use of compensatory mechanisms to overcome the lack of paretic propulsion. For example, Combs et al[33] reported a greater contribution of the non-paretic, instead of the paretic leg to propulsion generation when stroke survivors increased their gait speed following training. Interestingly, most studies demonstrating gains in speed without changes in paretic propulsion did not specifically focus on propulsion. The primary outcomes of these studies were related to independent walking capacity[55] or gait performance[54]. In contrast, four out of five studies that did report concurrent improvements in speed and propulsion specified both primary aim and primary outcome at the level of paretic propulsion[32,34,36,37]. These findings suggest that improvements in paretic propulsion do not merely emerge as a by-product of generic gait training, but require intervention strategies that specifically focus on this particular aspect of gait.

The improvement in paretic propulsive impulse was caused by an increase in both constituents of propulsion: the trailing limb angle[8-10] and the ankle plantarflexion moment[7,8]. Larger trailing limb angles yield a better biomechanical position for propulsion generation by the ankle muscles[9], as the ground reaction force is directed more anteriorly[11]. In the current training, we applied several methods aimed at increasing the trailing limb angle. When participants walked with reduced hip extension, guidance force was applied to help them match the hip extension reference trajectory of the robot. In addition, participants were encouraged to increase their paretic trailing limb angle by walking with increased step length or gait speed. Apart from the trailing limb angle, ankle plantarflexion moment also increased. In the current training, the use of ankle plantarflexion capacity was challenged by increasing gait speed and by imposing a robotic resistance that the participants had to move against. In addition to the supervised training, part of the exercises that participants performed at home were focused on bilaterally improving calf muscle strength. It therefore remains unclear whether the observed increase in ankle moment was due to the task-specific training in the robotic gait trainer, the muscle strengthening exercises, or a combination of both. Yet, previous studies that involved strength training did not find differences in post-stroke ankle kinetics[14,56]. We therefore consider the task-specific gait training to have been a key contributor to the observed increase in ankle plantarflexion moments.

The improvements in paretic propulsion are presumably unrelated to 'true' neurobiological recovery, as restitution of function is not expected to occur in the chronic phase[57]. In this phase, improvements in motor performance often result from learning new strategies to compensate for the existing impairments of the paretic limb[58]. For instance, stroke survivors may exaggerate propulsion of the *non-paretic* leg during gait[12,19]. Yet, it is difficult to reconcile the observed improvements in *paretic* propulsion with a compensatory mechanism. Here, remission of 'learned non-use' seems to be a more plausible explanation. Learned non-use is a phenomenon associated with damage to the nervous system, in which the initial inability to perform movements with the paretic limb in the acute phase, and subsequent slow recovery at the neural level, result in difficulties in paretic limb motor performance, leading to a conditioned suppression of the use of the paretic limb[59,60]. The notion of learned non-use implies the existence of latent, residual capacity of the paretic limb, which can be reduced by intensive, targeted training of the paretic limb[60,61]. The improvements in paretic propulsion that we observed following task-specific gait training are in line with this notion.

As not every stroke survivor may have such latent residual paretic capacity[62], it would be of interest to identify – prior to the intervention – which individuals do and may thus benefit most. We indeed found that participants with greater propulsive asymmetry at baseline showed larger treatments gains in propulsion symmetry. We also tested whether the baseline propulsion capacity score was associated with post-intervention gains in propulsion, but we could not confirm this previously reported relationship[39]. Nevertheless, both these potential determinants can only be tested in a gait laboratory, which may not be practical for clinical implementation. As identifying those individuals who may benefit most from training may help improve individually-tailored rehabilitation, future research should focus on establishing simple baseline measures as reliable indicators of residual propulsive capacity of the paretic leg.

In addition to gains in paretic propulsion, we also expected to find training-induced improvements in peak paretic knee flexion in those participants with reduced knee flexion at baseline, as it is known that propulsion generation provides mechanical energy to flex the leg during swing[63,64]. Although the difference just failed to reach statistical significance, it should be noted that following training peak knee flexion of the paretic leg had increased by almost 10 degrees and, thereby, exceeded the minimal detectable change for peak knee flexion (i.e. 5.7° [65]) and the minimal clinically important difference for knee sagittal range of motion in stroke survivors (i.e. 8.48° [66]). As improved post-stroke knee kinematics may promote safe foot clearance[12], it might be interesting for future studies to investigate intervention effects on both propulsion and knee kinematics in a larger group of stroke survivors with reduced knee flexion during swing at baseline.

Beneficial effects of training were not only observed in gait kinematics and kinetics, but also pertained to performance of functional gait tasks and, importantly, daily-life walking activity levels. Maintaining sufficient levels of physical activity in daily life is of vital importance for stroke survivors, as it is one of the cornerstones of cardiovascular risk management[67]. Although following our intervention the total *time* of walking remained constant, the *intensity* of walking had significantly increased. The intensity of walking, measured by accelerometer counts, is known to increase with faster gait speed[68-70]. Our findings thus indicate that the increase in gait speed, as measured in our laboratory, also translated to walking in daily life.

A limitation of the current proof-of-concept study is that we did not include a control group. Yet, by conducting two baseline assessments (separated in time by five weeks), we were able to increase the likelihood that improvements in propulsion symmetry were indeed attributable to the intervention period. Another study limitation is the relatively small range of lower extremity motor impairments in our group of participants, thereby limiting the generalizability of the current findings to the stroke population at large. People with more severe post-stroke motor impairments often have profound propulsion asymmetry, but it is conceivable that they also have limited residual propulsion capacity. Indeed, a previous study found that these individuals experienced lower gains in outcome after intervention[32]. Our finding that greater propulsion asymmetry at baseline was associated with larger intervention effects in propulsion symmetry may, therefore, not be generalized to stroke survivors with more severe motor impairments.

Conclusion

The finding that propulsion symmetry, gait speed, performance on functional gait tasks, and daily-life walking intensity had improved following task-specific training and persisted at follow-up hold promise for gait rehabilitation in individuals in the chronic phase after stroke. Future work should focus on identifying individuals with a latent propulsive capacity using simple measures at baseline, and confirm benefits of the used training concepts, in gait training settings with or without the use of an expensive robotic gait trainer, in a randomized controlled trial.

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References

1. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1995;76(1):27-32.
2. Olney SJ, Richards C. Hemiparetic gait following stroke. Part I: Characteristics. Gait Posture. 1996;4(2):136-148.
3. Perry J, Garrett M, Gronley JK, Mulroy SJ. Classification of walking handicap in the stroke population. Stroke. 1995;26(6):982-989.
4. Van de Port IG, Kwakkel G, Lindeman E. Community ambulation in patients with chronic stroke: how is it related to gait speed? J Rehabil Med. 2008;40(1):23-27.
5. Grau-Pellicer M, Chamarro-Lusar A, Medina-Casanovas J, Serda Ferrer BC. Walking speed as a predictor of community mobility and quality of life after stroke. Top Stroke Rehabil. 2019;26(5):349-358.
6. Schmid A, Duncan PW, Studenski S, et al. Improvements in speed-based gait classifications are meaningful. Stroke. 2007;38(7):2096-2100.
7. Farris DJ, Hampton A, Lewek MD, Sawicki GS. Revisiting the mechanics and energetics of walking in individuals with chronic hemiparesis following stroke: from individual limbs to lower limb joints. J Neuroeng Rehabil. 2015;12:24.
8. Hsiao H, Knarr BA, Higginson JS, Binder-Macleod SA. The relative contribution of ankle moment and trailing limb angle to propulsive force during gait. Hum Mov Sci. 2015;39:212-221.
9. Peterson CL, Cheng J, Kautz SA, Neptune RR. Leg extension is an important predictor of paretic leg propulsion in hemiparetic walking. Gait Posture. 2010;32(4):451-456.
10. Turns LJ, Neptune RR, Kautz SA. Relationships Between Muscle Activity and Anteroposterior Ground Reaction Forces in Hemiparetic Walking. Arch Phys Med Rehabil. 2007;88(9):1127-1135.
11. Tyrell CM, Roos MA, Rudolph KS, Reisman DS. Influence of systematic increases in treadmill walking speed on gait kinematics after stroke. Phys Ther. 2011;91(3):392-403.
12. Chen G, Patten C, Kothari DH, Zajac FE. Gait differences between individuals with post-stroke hemiparesis and non-disabled controls at matched speeds. Gait Posture. 2005;22(1):51-56.
13. Jonsdottir J, Recalcati M, Rabuffetti M, Casiraghi A, Boccardi S, Ferrarin M. Functional resources to increase gait speed in people with stroke: strategies adopted compared to healthy controls. Gait Posture. 2009;29(3):355-359.
14. Teixeira-Salmela LF, Nadeau S, McBride I, Olney SJ. Effects of muscle strengthening and physical conditioning training on temporal, kinematic and kinetic variables during gait in chronic stroke survivors. J Rehabil Med. 2001;33(2):53-60.
15. Mulroy S, Gronley J, Weiss W, Newsam C, Perry J. Use of cluster analysis for gait pattern classification of patients in the early and late recovery phases following stroke. Gait Posture. 2003;18(1):114-125.
16. Nadeau S, Gravel D, Arsenault AB, Bourbonnais D. Plantarflexor weakness as a limiting factor of gait speed in stroke subjects and the compensating role of hip flexors. Clin Biomech (Bristol, Avon). 1999;14(2):125-135.
17. Chen CL, Chen HC, Tang SF, Wu CY, Cheng PT, Hong WH. Gait performance with compensatory adaptations in stroke patients with different degrees of motor recovery. Am J Phys Med Rehabil. 2003;82(12):925-935.
18. Hsiao H, Gray VL, Creath RA, Binder-Macleod SA, Rogers MW. Control of lateral weight transfer is associated with walking speed in individuals post-stroke. J Biomech. 2017;60:72-78.
19. Bowden MG, Balasubramanian CK, Neptune RR, Kautz SA. Anterior-posterior ground reaction forces as a measure of paretic leg contribution in hemiparetic walking. Stroke. 2006;37(3):872-876.
20. Awad LN, Binder-Macleod SA, Pohlig RT, Reisman DS. Paretic Propulsion and Trailing Limb Angle Are Key Determinants of Long-Distance Walking Function After Stroke. Neurorehabil Neural Repair. 2015;29(6):499-508.
21. Roelker SA, Bowden MG, Kautz SA, Neptune RR. Paretic propulsion as a measure of walking performance and functional motor recovery post-stroke: A review. Gait Posture. 2019;68:6-14.
22. Campanini I, Merlo A, Damiano B. A method to differentiate the causes of stiff-knee gait in stroke patients. Gait Posture. 2013;38(2):165-169.
23. Piazza SJ, Delp SL. The influence of muscles on knee flexion during the swing phase of gait. J Biomech. 1996;29(6):723-733.
24. Abdulhadi HM, Kerrigan DC, LaRaia PJ. Contralateral shoe-lift: effect on oxygen cost of walking with an immobilized knee. Arch Phys Med Rehabil. 1996;77(7):670-672.
25. Lewek MD, Osborn AJ, Wutzke CJ. The influence of mechanically and physiologically imposed stiff-knee gait patterns on the energy cost of walking. Arch Phys Med Rehabil. 2012;93(1):123-128.
26. Weerdesteyn V, De Niet M, Van Duijnhoven HJR, Geurts ACH. Falls in individuals with stroke. J Rehabil Res Dev. 2008;45(8):1195-1214.
27. Raja B, Neptune RR, Kautz SA. Coordination of the non-paretic leg during hemiparetic gait: expected and novel compensatory patterns. Clin Biomech (Bristol, Avon). 2012;27(10):1023-1030.
28. Reisman DS, Binder-MacLeod S, Farquhar WB. Changes in metabolic cost of transport following locomotor training poststroke. Top Stroke Rehabil. 2013;20(2):161-170.
29. Awad LN, Lewek MD, Kesar TM, Franz JR, Bowden MG. These legs were made for propulsion: advancing the diagnosis and treatment of post-stroke propulsion deficits. J Neuroeng Rehabil. 2020;17(1):139.
30. Alingh JF, Groen BE, Van Asseldonk EHF, Geurts ACH, Weerdesteyn V. Effectiveness of rehabilitation interventions to improve paretic propulsion in individuals with stroke - A systematic review. Clin Biomech (Bristol, Avon). 2020;71:176-188.
31. Awad LN, Hsiao H, Binder-Macleod SA. Central Drive to the Paretic Ankle Plantarflexors Affects the Relationship Between Propulsion and Walking Speed After Stroke. J Neurol Phys Ther. 2020;44(1):42-48.
32. Awad LN, Reisman DS, Kesar TM, Binder-Macleod SA. Targeting Paretic Propulsion to Improve Poststroke Walking Function: A Preliminary Study. Arch Phys Med Rehabil. 2014;95(5):840-848.
33. Combs SA, Dugan EL, Ozimek EN, Curtis AB. Effects of body-weight supported treadmill training on kinetic symmetry in persons with chronic stroke. Clin Biomech. 2012;27(9):887-892.
34. Forrester LW, Roy A, Hafer-Macko C, Krebs HI, Macko RF. Task-specific ankle robotics gait training after stroke: a randomized pilot study. J Neuroeng Rehabil. 2016;13(1):51.
35. Hase K, Suzuki E, Matsumoto M, Fujiwara T, Liu MG. Effects of Therapeutic Gait Training Using a Prosthesis and a Treadmill for Ambulatory Patients With Hemiparesis. Arch Phys Med Rehabil. 2011;92(12):1961-1966.
36. Hsiao H, Awad LN, Palmer JA, Higginson JS, Binder-Macleod SA. Contribution of Paretic and Nonparetic Limb Peak Propulsive Forces to Changes in Walking Speed in Individuals Poststroke. Neurorehabil Neural Repair. 2016;30(8):743-752.
37. Reisman D, Kesar T, Perumal R, et al. Time Course of Functional and Biomechanical Improvements During a Gait Training Intervention in Persons With Chronic Stroke. J Neurol Phys Ther. 2013;37(4):159-165.
38. Meuleman J, Van Asseldonk E, Van Oort G, Rietman H, Van der Kooij H. LOPES II--Design and Evaluation of an Admittance Controlled Gait Training Robot With Shadow-Leg Approach. IEEE Trans Neural Syst Rehabil Eng. 2016;24(3):352-363.
39. Hsiao H, Higginson JS, Binder-Macleod SA. Baseline predictors of treatment gains in peak propulsive force in individuals poststroke. J Neuroeng Rehabil. 2016;13:2.
40. Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. Phys Ther. 1984;64(1):35-40.
41. Medical Research Council (Great Britain). Aids to the examination of the peripheral nervous system. 1st ed. London: HM Stationery Office; 1976.
42. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-198.

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43. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-370.
44. Wilson B, Cockburn J, Halligan P. Development of a behavioral test of visuospatial neglect. Arch Phys Med Rehabil. 1987;68(2):98-102.
45. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther. 1987;67(2):206-207.
46. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scand J Rehabil Med. 1975;7(1):13-31.
47. Demeurisse G, Demol O, Robaye E. Motor evaluation in vascular hemiplegia. Eur Neurol. 1980;19(6):382-389.
48. Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J. 1985;132(8):919-923.
49. Wrisley DM, Marchetti GF, Kuharsky DK, Whitney SL. Reliability, internal consistency, and validity of data obtained with the functional gait assessment. Phys Ther. 2004;84(10):906-918.
50. Duncan PW, Bode RK, Min Lai S, Perera S. Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale. Arch Phys Med Rehabil. 2003;84(7):950-963.
51. Fanchamps MHJ, Horemans HLD, Ribbers GM, Stam HJ, Bussmann JBJ. The Accuracy of the Detection of Body Postures and Movements Using a Physical Activity Monitor in People after a Stroke. Sensors (Basel). 2018;18(7):950-963.
52. Perry J, Burnfield JM. Gait Analysis: Normal and Pathological Function. 2nd ed. Thorofare: SLACK Incorporated; 2010: pp. 531-534.
53. Sheffler LR, Taylor PN, Bailey SN, et al. Surface peroneal nerve stimulation in lower limb hemiparesis: effect on quantitative gait parameters. Am J Phys Med Rehabil. 2015;94(5):341-357.
54. Routson RL, Clark DJ, Bowden MG, Kautz SA, Neptune RR. The influence of locomotor rehabilitation on module quality and post-stroke hemiparetic walking performance. Gait Posture. 2013;38(3):511-517.
55. Yeung LF, Ockenfeld C, Pang MK, et al. Randomized controlled trial of robot-assisted gait training with dorsiflexion assistance on chronic stroke patients wearing ankle-foot-orthosis. J Neuroeng Rehabil. 2018;15(1):51.
56. Milot M-H, Nadeau S, Gravel D, Bourbonnais D. Gait Performance and Lower-Limb Muscle Strength Improved in Both Upper-Limb and Lower-Limb Isokinetic Training Programs in Individuals with Chronic Stroke. ISRN Rehabil. 2013;2013(1):1-10.
57. Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. Restor Neurol Neurosci. 2004;22(3-5):281-299.
58. Buma F, Kwakkel G, Ramsey N. Understanding upper limb recovery after stroke. Restor Neurol Neurosci. 2013;31(6):707-722.
59. Taub E. Movement in nonhuman primates deprived of somatosensory feedback. Exerc Sport Sci Rev. 1976;4:335-374.
60. Taub E, Uswatte G, Mark VW, Morris DM. The learned nonuse phenomenon: implications for rehabilitation. Eura Medicophys. 2006;42(3):241-256.
61. Mark VW, Taub E. Constraint-induced movement therapy for chronic stroke hemiparesis and other disabilities. Restor Neurol Neurosci. 2004;22(3-5):317-336.
62. Bowden MG, Behrman AL, Neptune RR, Gregory CM, Kautz SA. Locomotor rehabilitation of individuals with chronic stroke: difference between responders and nonresponders. Arch Phys Med Rehabil. 2013;94(5):856-862.
63. Lipfert SW, Günther M, Renjewski D, Seyfarth A. Impulsive ankle push-off powers leg swing in human walking. J Exp Biol. 2014;217:1218-1228.
64. Neptune RR, Kautz SA, Zajac FE. Contributions of the individual ankle plantar flexors to support, forward progression and swing initiation during walking. J Biomech. 2001;34(11):1387-1398.
65. Kesar TM, Binder-Macleod SA, Hicks GE, Reisman DS. Minimal detectable change for gait variables collected during treadmill walking in individuals post-stroke. Gait Posture. 2011;33(2):314-317.
66. Guzik A, Drużbicki M, Wolan-Nieroda A, Turolla A, Kiper P. Estimating Minimal Clinically Important Differences for Knee Range of Motion after Stroke. J Clin Med. 2020;9(10):3305.
67. Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Exerc. 2009;41(7):1510-1530.
68. De Groot S, Nieuwenhuizen MG. Validity and reliability of measuring activities, movement intensity and energy expenditure with the DynaPort MoveMonitor. Med Eng Phys. 2013;35(10):1499-1505.
69. Tweedy SM, Trost SG. Validity of accelerometry for measurement of activity in people with brain injury. Med Sci Sports Exerc. 2005;37(9):1474-1480.
70. Braakhuis HEM, Roelofs JMB, Berger MAM, Ribbers GM, Weerdesteyn V, Bussmann JBJ. Intensity of daily physical activity - a key component for improving physical capacity after minor stroke? Disabil Rehabil. 2020:1-6.

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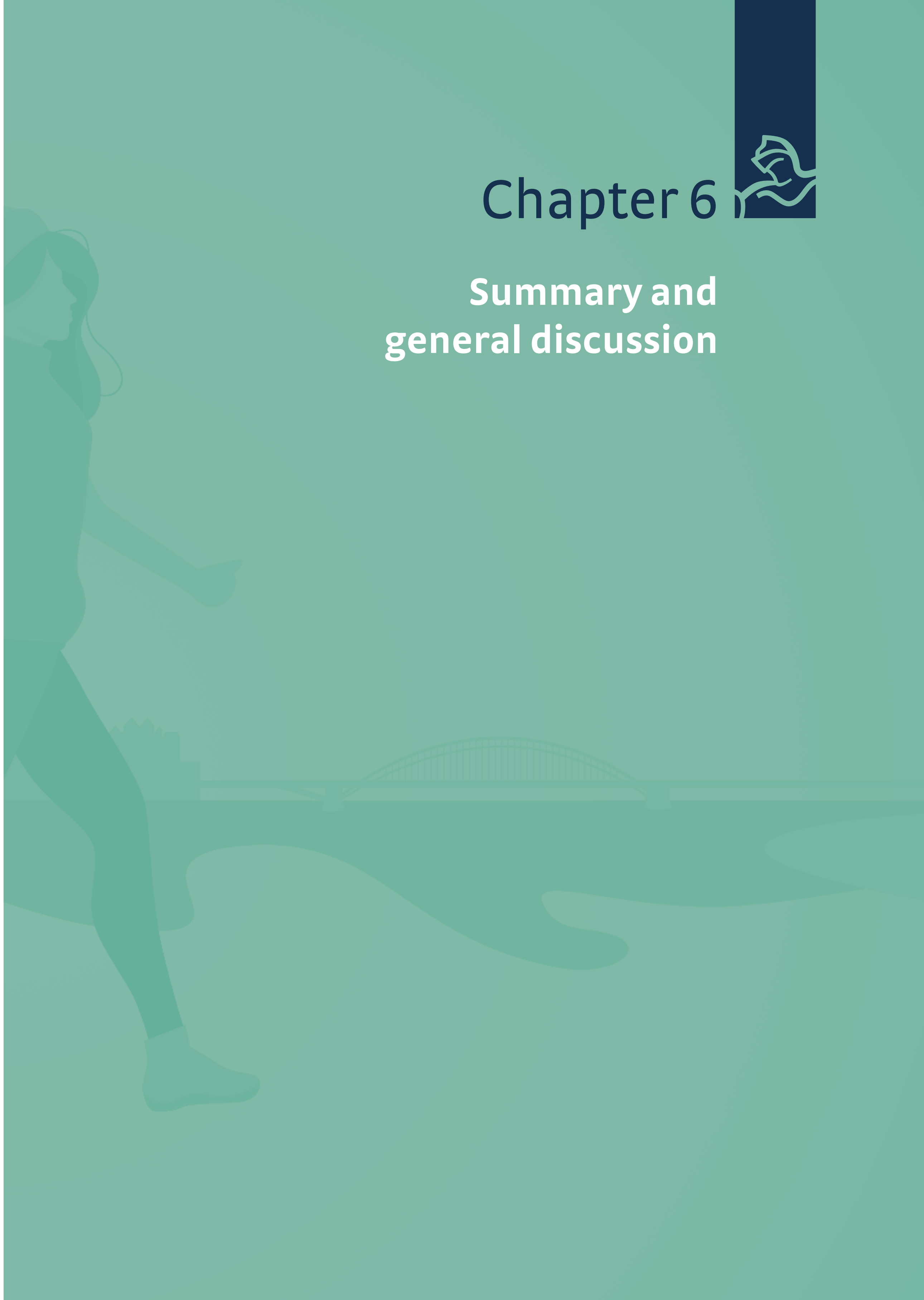
Supplementary files

Table S1. Results of the mixed model analyses

	Baseline (average T0 and T1) vs. post-intervention (average T2 and T3)	Interaction T0 * post-intervention (average T2 and T3)	T2 vs. T3
Propulsion measures			
Propulsive impulse			
Symmetry	F(79.392)=36.032 p<0.001	F(79.499)=18.199 p<0.001	F(77.489)=3.083 p=0.083
Paretic leg	F(103.511)=4.730 p=0.032	F(102.641)=1.794 p=0.183	F(75.092)=0.010 p=0.922
Non-paretic leg	F(103.629)=1.738 p=0.190	F(103.817)=0.733 p=0.394	F(75.780)=0.125 p=0.724
Trailing limb angle – paretic leg	F(92.916)=26.025 p<0.001	F(94.000)=23.347 p<0.001	F(79.246)=1.129 p=0.291
Ankle plantarflexion moment – paretic leg	F(103.739)=10.173 p=0.002	F(103.291)=7.271 p=0.008	F(77.532)=0.379 p=0.540
Capacity measures			
Gait speed	F(97.658)=19.430 p<0.001	F(97.875)=14.402 p<0.001	F(81.464)=3.954 p=0.050
6MWT	F(103.389)=8.671 p=0.004	F(103.903)=2.122 p=0.148	F(81.368)=0.306 p=0.582
FGA	F(100.612)=5.694 p=0.019	F(100.888)=1.823 p=0.180	F(77.617)=1.870 p=0.175
Mobility at home			
SIS – Mobility	F(99.999)=2.091 p=0.151	F(99.773)=3.682 p=0.058	F(62.619)=2.464 p=0.122
Activ8 walking			
Total time	F(99.794)=2.636 p=0.108	F(100.958)=0.794 p=0.375	F(81.263)=0.092 p=0.762
Total intensity	F(98.325)=9.142 p=0.003	F(98.899)=3.752 p=0.056	F(82.304)=0.468 p=0.496

6MWT: 6-Minute Walk Test; FGA: Functional Gait Assessment; SIS: Stroke Impact Scale.



Chapter 6

Summary and general discussion

Summary

The rehabilitation of gait after stroke is an important topic in neurorehabilitation both from a clinical and scientific perspective. To improve post-stroke gait rehabilitation, robotic gait trainers are increasingly recommended and applied. Control of pelvic movements is an important determinant of gait, and restoring normal pelvic movement patterns therefore seems a crucial goal in gait training after stroke. Yet, surprisingly, some robotic gait trainers constrain the pelvic movements. Therefore, in Chapter 2, we investigated the immediate after-effects of a single session of robotic gait training with either mechanically constrained or supported degrees of freedom around the pelvis on the overground gait pattern in healthy adults. Constraining both the lateral displacements and rotations of the pelvis during robotic gait resulted in a smaller lateral pelvic displacement and step width during the first five steps of overground walking following the robotic gait training session, when compared to the immediate after-effects of a robotic gait training session during which the lateral pelvic displacements were actively guided by the LOPES II and pelvic rotations were free. The reduced lateral pelvic displacement and step width returned to baseline values within 10 steps of overground gait. Kinematics and other spatiotemporal parameters were not affected by either the pelvic constraint or support condition. In healthy adults, robotic gait training with constrained pelvic movements thus had immediate, short-lived negative after-effects on the overground gait pattern, whereas robotic gait training including support of more degrees of freedom around the pelvis better resembled the natural gait pattern.

In Chapter 3, the results of a two-center, assessor-blinded, randomized controlled trial were presented, in which the effects of six weeks robotic gait training with an assist-as-needed approach and multiple degrees of freedom (AAN_{mDOF}) in the LOPES II on the gait pattern were compared to conventional gait training in subacute stroke survivors (<10-weeks post onset, Functional Ambulation Categories 3-5). The training focused on improving pre-defined training goals related to the individual's gait impairments, including better foot clearance, knee stability in stance, limb loading or foot prepositioning. In both groups, external mechanical work had decreased between baseline (T0) and the end of training (T1), and had become similar to T0 at 4-months follow-up (T2), whereas gait speed had increased at both assessments relative to baseline. Furthermore, both groups improved most spatiotemporal gait parameters, functional gait tasks, and clinical scores at T1 and T2, relative to T0. Apart from increased step width following conventional gait training at T1 and larger paretic step length following AAN_{mDOF} robotic gait training at T2, no significant differences between both groups were observed at T1 or T2 compared to T0. Participants with a pre-defined training goal aimed at improving foot clearance (N=12) improved their paretic knee flexion more following AAN_{mDOF} robotic gait training compared to conventional gait training, whereas no difference between the training effect was observed for participants with a pre-defined training goal aimed at improving knee stability in stance (N=13). Due to the small number of participants, no group comparisons were made for outcomes related to the pre-defined training goals aimed at improving limb loading (N=6) or foot prepositioning (N=1). In general, AAN_{mDOF} robotic gait training was not superior to conventional training for improving the quality of the gait pattern in subacute stroke survivors after the training period and at four months follow-up, but it was concluded that AAN_{mDOF} robotic gait training might be more effective for improving specific gait abnormalities, such as knee flexion during swing, in stroke survivors (see Box 1, case 1).

In Chapter 4, a systematic overview of the potential effectiveness of post-stroke rehabilitation interventions for improving paretic propulsion, ankle kinetics, and gait speed in subacute and chronic stroke survivors was provided. Interventions included exercise interventions (N=25), surgical interventions (N=2), and non-invasive brain stimulation (N=1). Propulsion measures were the primary outcome in eight studies. Six studies were found to be of high quality. In general, mixed results were reported for intervention effects on propulsion and ankle kinetics, with 14 studies yielding improvements in propulsion and/or ankle kinetics. In contrast, gains in gait speed were reported in the vast majority of studies (N=20 out of 23). Gains in propulsion were observed following interventions that challenged and/or enabled the utilization of latent propulsive capacity of the paretic leg during gait. As gait speed generally increased regardless of the observed change in propulsion, this finding suggests the use of compensatory strategies to increase speed in most stroke survivors.

Chapter 5 elaborates on the findings in Chapter 4 by presenting the results of a five-week robotic gait training (60 minutes, twice a week) in the LOPES II for improving propulsion symmetry by increasing paretic propulsion in chronic stroke survivors. In addition to the robotic gait training, participants performed daily home exercises (15 minutes/day) focusing on increasing calf muscle strength and practicing the learned strategies in daily life. Propulsion measures, gait kinematics and kinetics, self-selected gait speed, performance of functional gait tasks, and daily-life mobility and physical activity were determined at each assessment (five weeks (T0) and one week (T1) before the start of the intervention, and one week (T2) and five weeks (T3) after the intervention period). Between T0 and T1, none of the outcomes had significantly changed, except for an increase in gait speed. Following the intervention, a significant improvement in propulsion symmetry and paretic propulsive impulse was observed, whereas the non-paretic propulsive impulse remained unchanged. Greater improvements in propulsion symmetry were observed in participants with more severe asymmetrical propulsion at T0. In addition, paretic leg's trailing limb angle and ankle plantarflexion moment had significantly increased following the intervention. Furthermore, significant increases in gait speed, 6-Minute Walk Test, Functional Gait Assessment, and daily-life walking intensity were observed following the intervention. The gains in all outcome measures were retained at five-week follow-up, and gait speed had further increased at this point in time. These results suggest that robotic gait training may be effective to utilize latent propulsive capacity of the paretic leg in individuals in the chronic phase after stroke, thereby not only increasing propulsion symmetry and gait speed, but also improving the performance of functional gait tasks and walking activity levels in daily life (see Box 1, case 2).

Box 1. Follow-up of cases described in general introduction (page 17)

Case 1

The 55-year old woman participated in a 5-week robotic gait training with LOPES II, focusing on improving her knee stability during the stance phase of gait. It took her some time to get used to walking in the device but, once she became familiar with it, she appreciated to re-experience the feeling of 'normal walking'. After she had completed the 5-week LOPES II training using an assist-as-needed (AAN) approach, she was able to walk in- and outdoors without a walking aid. She used a walker only for long distances. In addition, she had improved her self-selected gait speed (+68%) and endurance (walking distance +76%), she had reduced her external mechanical work (-21%) and she showed a lower maximum paretic knee extension velocity, indicating better paretic knee stability in the stance phase. At 4-months follow-up, she had retained her improved knee stability. Her external mechanical work had slightly increased (+8%), but her gait speed (+16%) and endurance (+19%) had further improved. She was very satisfied with her gait recovery but, unfortunately, shoulder pain had developed over time, which forced her to adjust her activity level.

Case 2

The 58-year old man completed a 6-week robotic gait training with LOPES II, focusing on improving paretic leg propulsion. Even though he found the training quite 'tough', he successfully completed the LOPES II training and home exercises. At the end of the robotic gait training intervention, he had improved his paretic propulsion by 8.6%, resulting in a more symmetrical propulsion. Furthermore, he had increased his gait speed (+7.4%) and endurance (+6.8%), and also the intensity of his daily life walking activities (+7.5%). At 5-weeks follow-up, he had retained the gain in all outcomes. At home, he walked longer distances at a faster pace without a walking aid, but he still used a cane for walking on uneven surfaces such as a sandy path. His friends and family reported that he was better able to maintain a conversation while walking and appeared less fatigued afterwards.

General discussion

This thesis focused on the potential benefits of robotic gait training in the LOPES II for improving the gait pattern of individuals in the subacute or chronic phase post stroke. Such benefits of gait training in the LOPES II were expected because of two key features of the device: 1) the assist-as-needed approach and 2) the mechanical support of multiple degrees of freedom in both the frontal and sagittal planes. This allows the LOPES II to apply minimal levels of support – promoting active participation – to specific, impaired aspects of the hemiparetic gait pattern. It also allows providing feedback on performance of selected gait parameters. Post-stroke gait training in the LOPES II thus complies with key principles of motor rehabilitation, and the work in this thesis aimed to provide evidence for its effectiveness.

In this general discussion section, I will reflect on the insights generated by the studies presented in the previous chapters, along the following lines:

- Are multiple mechanically-supported degrees of freedom in the LOPES II important for transferring training effects to overground gait? (Chapter 2)
- Does robotic gait training improve the gait pattern in individuals with stroke? (Chapter 3, 4 and 5)
- Which mechanisms may underlie the observed effects?
- What are the future perspectives of robotic gait training post stroke?

Do additional mechanically-supported degrees of freedom have merits?

In this thesis, we first examined in healthy individuals whether assisting pelvic movements during robotic gait training transferred to different overground gait patterns compared to training with constrained pelvic movements. This is an important question, because many robotic gait training devices that are currently in use lack the option of supporting pelvic movements. From a motor learning perspective, recreating normal pelvic movements seems instrumental for achieving optimal training outcomes. Performing the desired movements during gait training will optimize proprioceptive feedback provided to the nervous system[1], which is commonly held to play an important role in motor learning[2]. Allowing pelvic movements during robotic gait training will enable proper weight shifting and limb loading, and may challenge balance just like required during overground gait. Conversely, repetitive practice of a movement that does not represent the requirements for overground gait, such as restricting pelvic displacement during gait, may potentially lead to adoption of maladaptive compensatory strategies. The latter should be prevented, especially when considering the increased use of robotic gait training for relearning and improving gait in neurological patients.

Previous studies reported altered gait kinematics during unconstrained *treadmill* walking after (robotic) gait training with restricted pelvic degrees of freedom[3,4], suggesting that allowing additional degrees of freedom around the pelvis may be better. The results reported in Chapter 2 indeed showed a small beneficial effect of extra degrees of freedom around the pelvis on the *overground* gait pattern in healthy young adults. Although the after-effects were short-lived and have yet to be studied in neurological patients, these results provide supporting evidence for the notion that robotic gait trainers should allow pelvic movement assistance for training a gait pattern that best resembles the targeted overground gait pattern. Thus far, only robotic gait trainers used in research environments provide these options[5,6]. The commercially available robotic gait trainer Lokomat FreeD (Hocoma AG, Volketswil, Switzerland) allows the pelvis to move in the frontal and transversal planes, but mechanical support of these degrees of freedom is not yet possible and could be a recommendation for future development.

Effects of robotic gait training on the post-stroke gait pattern

In the second part of this thesis we evaluated the efficacy of robotic gait training with multiple degrees of freedom and an assist-as-needed approach in people after stroke with regard to *gait capacity* and *gait pattern*, the latter being the main novelty of our work. Regarding the effects on *gait capacity*, in subacute ambulatory stroke survivors we observed higher gait speeds and endurance after robotic gait training compared to before, but these effects were not yet superior to conventional gait training (Chapter 3). Our work thus confirms the findings of previous randomized controlled trials in ambulatory subacute stroke survivors that also reported robotic gait training being as effective as conventional gait training in improving gait speed[7-9] and endurance[8]. Similarly, other gait capacity outcomes, i.e. gait independence, also failed to demonstrate superior effects of robotic gait training in ambulatory stroke survivors in the subacute phase[7], whereas Hidler et al (2009) even reported greater improvements in gait speed and endurance following conventional gait training[10]. Hence, regarding improvements in gait capacity, robotic and conventional gait training interventions appear to be equally effective in the subacute phase. We found no supporting evidence for the added value of the applied assist-as-needed approach and the additional degrees of freedom of the LOPES II.

In the chronic phase after stroke, greater gains in gait speed and endurance have been reported following robotic compared to conventional gait training in ambulatory individuals[11-17], yet several other studies did not confirm these results[18-22]. In our study in chronic stroke survivors (Chapter 5), we did observe a significant increase in gait speed and endurance following training, but the lack of a control group precluded drawing conclusions on the possible superiority of our robotic gait training for this gait capacity outcome. Indeed, previous work[23-25] and the results of our systematic review (Chapter 4) demonstrate that many types of intervention have the potential of improving gait speed in the chronic phase post stroke. What the results in Chapter 4 also demonstrated is that training-induced gains in gait speed may be achieved by different strategies (i.e. changes in the gait pattern), thus indicating different modes of action of the varying types of intervention. However, such differential effects of training cannot be distinguished by generic gait capacity outcomes. Owing to the multiple degrees of freedom and an assist-as-needed approach of LOPES II, we hypothesized that the mode of action of our robotic gait training would be different from conventional gait training, and different types of outcome measures (i.e. at the level of the gait pattern) may thus be needed to demonstrate the potential added value of our robotic gait training. In the following paragraphs, I will reflect on the insights that we gained from using these *gait pattern* outcomes regarding the expected benefits of robotic gait training in LOPES II.

Evaluating the effect of training on the post-stroke gait pattern is a challenge as the hemiparetic gait pattern is typically characterized by a wide, interindividual variability in kinetic and kinematic gait impairments, and individual training goals therefore aim at improving different aspects of the gait pattern. To evaluate the effectiveness of robotic gait training on the gait pattern at the group level, we thus need an outcome measure that captures changes in all these different aspects of the hemiparetic gait pattern that can be targeted during training. In Chapter 3 of this thesis, external mechanical work was used for this purpose, as it represents whole body mechanics, and was expected to be sensitive enough to detect improvements in the different aspects of the individual gait patterns. For instance, previous uncontrolled studies with small sample sizes reported lower mechanical work following gait training that decreased the vertical displacement of the body's center of mass[26], and following intramuscular botulinum toxin injections to reduce stiff-knee gait[27]. The results in Chapter 3 indeed showed significant improvements in external mechanical work following training, yet no differential effects could be demonstrated between our robotic and conventional gait training interventions. This either indicates that our robotic gait training may not have had any surplus value for improving the post-stroke gait pattern in the subacute phase – despite the LOPES II allowing selective support of specific impaired subtasks of gait – or that the external work outcome may not have been sensitive enough to pick up (relatively modest) differential training effects.

To shed light on this issue, we also evaluated kinematic gait parameters that were specific to the individual training goals. In these subgroup analyses, the effect of our robotic gait training on knee flexion during swing was found to be superior to conventional gait training in participants with poor knee flexion at baseline (Chapter 3). Previous work has shown improvements in post-stroke knee flexion angle during swing immediately following a single session of robotic gait training[28,29], and the work in this thesis importantly extends on these findings by demonstrating that such training-induced gains in knee flexion may be retained until at least four months after completion of the intervention. Yet, this clinically-relevant finding did not result in differential training effects in external mechanical work. Apparently, the greater improvements in knee flexion following our robotic gait training were too small and/or were present in too few participants to be reflected in our primary outcome. It shows that more specific outcome measures may indeed be needed to capture the potential added value of robotic gait training with an assist-as-needed approach and multiple mechanically-supported degrees of freedom in both the frontal and sagittal planes. Yet, it also highlights the difficult trade-off between using more generic (e.g. external work) versus specific outcomes (e.g. knee flexion during swing) when evaluating the effects of robotic gait training in a heterogeneous group of patients with varying training goals.

In our study in chronic stroke survivors (Chapter 5), recruiting a more homogeneous group of participants with asymmetric propulsion generation at baseline allowed to specifically evaluate the effects of robotic gait training on this aspect of the gait pattern. Here, the results demonstrated improvements in propulsion of the paretic leg following robotic gait training, which were retained until at least five weeks post intervention. Although this study did not include a comparison with a control intervention, there are two arguments supporting the conclusion that these effects can indeed be attributed to the robotic gait training. First, in the chronic phase post stroke, no spontaneous improvements in the gait pattern are to be expected, which was confirmed by the lack of changes in propulsion outcomes between the two baseline measurements that we conducted with five weeks in between. Second, the results of our systematic review (Chapter 4) showed that improvements in propulsion may only be expected when the intervention specifically targets this particular aspect of walking, which concurs with the notion that task specificity is key in motor rehabilitation after stroke. Hence, the results in Chapter 5 (and to a lesser extent, also the subgroup analysis on knee flexion angles during swing in Chapter 3) provide evidence for the effectiveness of robotic gait training for improving specific aspects of the gait pattern in stroke survivors. Robotic gait trainers, such as LOPES II, may be able to create an environment in which the pre-requisites for gait are facilitated, and participants can focus their attention on the specific subtasks of the gait pattern that are being trained, while maladaptive compensatory movements are prevented. In addition, these studies underscore the need for evaluation of specific outcome measures that reflect the patient-specific training goals.

Mechanisms underlying gait recovery after stroke

For promoting motor relearning after stroke, task-specific, high intensity and repetitive training is thought to be most effective[30]. Our robotic gait training interventions with LOPES II were designed with these key principles in mind and, as discussed above, we indeed found improvements in gait pattern outcomes. There are several mechanisms that may underlie motor recovery after stroke and, in this section, I will discuss which of these mechanisms may potentially explain the results of our two training studies.

In the subacute phase after stroke, behavioral restitution of function and behavioral substitution of function are considered to be the main mechanisms that drive motor relearning. Behavioral restitution of function refers to a return towards more normal patterns of motor control, while behavioral substitution of function refers to the learning and use of alternative, compensatory movements[31]. Generally, stroke survivors demonstrate at least some behavioral restitution of function early after stroke[32,33], mainly due to spontaneous neurological recovery. This process is most prominent in the first six weeks after stroke[34], and is known to be the result of re-activation of penumbral brain areas[35], resolution of diaschisis[36], or brain reorganization[37]. Recovery of *gait capacity* is known to rely not only on behavioral restitution, but also on substitution of function, as improvements in, for instance, gait speed and gait independence continue far beyond the time window of spontaneous neurological recovery. Recovery of the *gait pattern* in the subacute phase, however, appears to be driven (almost) exclusively by spontaneous neurological recovery, as the impairment in leg motor control is the key determinant of the leg muscle activation patterns during walking (and, thus, the gait pattern), and the (impaired) muscle activation patterns remain unchanged despite continued rehabilitation treatment[38,39].

Although there is yet little evidence for the effectiveness of training interventions for promoting behavioral restitution of function[40], in Chapter 3 we tested whether robotic gait training with the LOPES II may still have the potential to improve the gait pattern in the subacute phase, owing to the assist-as-needed approach and the multiple mechanically-supported degrees of freedom. In general, the lack of significant differences between conventional and robotic gait training in the observed gains in external mechanical work supports the notion that training interventions indeed appear to have little additional effects on behavioral restitution of function after stroke, beyond what can be expected from spontaneous neurological recovery. Yet, if this is true, how can we then understand the observed improvements in knee flexion angles during the swing phase in a subsample of our population following robotic gait training? As this kinematic change leads to a return towards a more normal gait pattern, it may be speculated that these effects indeed reflect a modest effect of robotic gait training on behavioral restitution of function. The robotic gait trainer may have provided an environment that reduced the chance of adopting maladaptive compensatory mechanisms, like hip pull off during swing, which may have allowed our participants to make optimal use of their restored paretic leg motor control. Our robotic gait training may thus have promoted behavioral restitution, not by directly affecting neurological recovery, but by reducing the relative contribution of maladaptive behavioral substitution. Yet, as the beneficial effects of robotic gait training on the gait pattern were only observed in a subsample of subacute stroke survivors with reduced knee flexion during swing, considerably more work is required to replicate these findings and establish the potential added value of robotic gait training on other aspects of the gait pattern.

In the chronic phase after stroke, the mechanisms that may contribute to changes in the gait pattern include behavioral substitution of function and remission of learned non-use. Remission of learned non-use implies additional functional recovery through the utilization of latent, residual motor capacity[41,42]. With respect to training-induced improvements in *gait capacity*, our systematic review (Chapter 4) demonstrated that gains in walking speed following training interventions were often achieved by the use of compensatory strategies to overcome deficient paretic push-off. On the other hand, there is growing evidence that some chronic stroke survivors have a latent residual propulsive capacity of the paretic leg, which use may be promoted by targeted and challenging training[29,43,44]. In our study in Chapter 5, we aimed to provide evidence for the benefits of robotic gait training for remitting learned non-use of paretic propulsive capacity, and our results indeed support this notion. This is an interesting finding, as it shows that targeted training that specifically focuses on utilization of latent capacity provides a promising avenue for improving the gait pattern in the chronic phase post stroke.

Future perspectives of robotic gait training post stroke

The robotic gait trainer used in all experimental studies of this thesis (i.e. LOPES II) is a medical device without CE-mark that cannot be used in clinical practice. CE-marking indicates that a product meets the European Union requirements for safety, health and environmental protection standards. For medical devices, CE-marking is mandatory to allow its use in clinical practice. Procedures to obtain a CE-mark via a Notified Body are generally time consuming and expensive. For new medical devices that are still under development and may need to undergo future design changes that can alter health and safety risks, it does not seem convenient to apply for a CE-mark yet, as the final design may require re-evaluation of the device by the Notified Body to (re)acquire an (expanded) CE-mark. Likewise, no CE mark was obtained for neither the LOPES I[45] nor the LOPES II[5]. Because LOPES II is a non-CE-marked medical device, and unfortunately, its further development and steps towards commercialization were discontinued during the project, it will not find its way to clinical practice. Although direct implementation of the current findings in clinical practice is therefore not possible, we believe that our results (particularly those in Chapter 3) may also apply to commercial robotic gait trainers with additional degrees of freedom, which are now starting to find their way to the clinic.

These new robotic gait trainers yet provide limited options for an assist-as-needed (AAN) approach, being another key feature of the LOPES II. The AAN approach – which implies that minimal levels of assistance are only provided when needed and participants are mostly in control of their own movements – is thought to promote active participation during robotic gait training. It is widely accepted that actively practicing a motor skill is far more effective than performing passive movements to improve motor function[46]. Previous research has shown that AAN robotic gait training indeed resulted in increased muscle activation[47] and energy consumption[48,49] when compared to walking in robotic gait trainers that use other assistance modalities. Yet, in Chapter 3 of this thesis we were unable to show a substantial benefit of AAN robotic gait training in subacute stroke survivors. In the work reported in Chapters 3 and 5, the therapists selected the (estimated) guidance force levels, which may have led to higher assistance levels than strictly needed. Indeed, the work of Fricke et al. (2020) has shown that therapists generally choose higher assistance levels than those predicted based on an automatically-tuned algorithm[50]. As levels of support are expected to decrease with the participant's progress, therapists should be aware to continuously adjust the level of support to the individual's needs in order to optimize active participation and potential gains in motor learning. Future robotic gait trainers may include embedded AAN algorithms to help therapists select the most optimal training setting. Further work is needed to establish whether this may translate to better training efficacy.

Limitations, methodological considerations, and future recommendations

The research presented in this thesis has some limitations that will be discussed here. First, we aimed to evaluate the effects of robotic gait training on the post-stroke gait pattern (i.e. mechanical work, propulsion and kinematics), which required participants to be able to take at least a few steps without physical support prior to the start of intervention. As such, the generalizability of our findings is limited to independent ambulatory stroke survivors (FAC≥3). Although most individuals in the chronic phase after stroke have regained their walking independence (81-85%)[51,52], only 27-37% of the acute stroke survivors admitted to inpatient rehabilitation can walk independently[51-53]. For improving *gait capacity*, previous systematic reviews[54-57] indicated that robotic gait training was especially effective in more severely affected stroke survivors with lower levels of functional ambulation (i.e. FAC≤2, physical support needed during gait[58]) in the early phase after stroke. Whether this also applies to the potential effects of robotic gait training on the *gait pattern* remains to be studied. The conduct of such future studies would be facilitated by establishing valid outcome measures for evaluating changes in the post-stroke gait pattern in dependent ambulators who rely on assistance of a person or walking aid.

Second, for the calculation of external mechanical work (as the primary outcome in Chapter 3), it would have been better to not only use kinematic data, but also use force plate recordings. Yet, it turned out to be very difficult for stroke survivors with very limited independent walking capacity to successfully hit force plates embedded in the ground surface during the gait analysis. As a result, ground reaction force data of too few steps were available for proper analysis of the center of mass (COM) movements. We therefore had to derive the COM movements from the kinematic data only. Although this has been demonstrated to be an accurate method[59], it does not allow distinguishing between the negative (i.e. energy loss) and positive (i.e. energy production) mechanical work performed by the leading and trailing limb during the double support phase. It has been shown by Donelan et al (2002) that this results in a substantial underestimation of the external mechanical work performed during gait[60]. This limitation of our external mechanical work calculation may have affected its sensitivity for detecting modest changes in the gait pattern.

Third, the present thesis focused on the relatively short-term after effects of robotic gait training on the overground gait pattern of stroke survivors. Hence, it remains to be determined whether the observed improvements in gait pattern are retained over a longer period of time (e.g. up to one year post intervention), and whether these improvements could sustainably contribute to improved activity levels in daily life and quality of life.

Clinical implications and concluding remarks

I would like to conclude by highlighting the clinical implications of the work in this thesis. Currently, evidence is lacking for conventional gait training being effective in improving the post-stroke gait pattern. Yet, the findings of this thesis suggest that there may still be some room for improvement, by preventing (in the subacute phase) or unlearning (in the chronic phase) maladaptive compensatory strategies and optimizing the use of residual paretic leg motor function. To do so, gait training should be provided in an environment in which the pre-requisites for achieving specific training goals are met, and in which stroke survivors can focus their attention on specific training goals. For instance, when the specific goal of training is to improve paretic foot clearance, the attentional load of maintaining balance may be reduced by providing adequate support while not impeding normal trunk movements. This may be difficult to achieve for physical therapists during conventional gait training, as it would require manual support of balance and trunk movements, while concurrently attending to the specific training goals related to the paretic leg. This is where rehabilitation technology appears to be most helpful, as it can create an environment that provides opportunities to train specific aspects of the gait pattern. Such technological options not only include robotic gait trainers, but also body-weight support systems such as the Zero-G or the Rysen, or systems that help control pelvic movements during treadmill walking.

Yet, given the costs of gait training interventions – particularly of those that apply advanced technology – it is important to determine which individuals are most likely to benefit from a specific type of training. The work in this thesis provides some insight into this matter. Based on the results of Chapter 3, robotic gait training may have a small additional benefit for stroke survivors with poor knee flexion during swing. Other than that, conventional gait training appears to remain a good standard of care for gait rehabilitation in the subacute phase after stroke. In the chronic phase after stroke, we were able to demonstrate that robotic gait training improved paretic propulsion in a group of well-selected individuals, but those with the largest degree of propulsion asymmetry at baseline improved most. Yet, we used a lab-based gait analysis to establish this asymmetry. A next step would be to translate this insight into a clinical testing method to identify individuals with latent, residual capacity who may benefit from training. Furthermore, as rehabilitation interventions for improving gait are not typically offered to individuals in the chronic phase after stroke, the question also arises whether we may need to reconsider stroke care provision in the chronic phase.

In conclusion, the work in this thesis provides new insights into how and for whom robotic gait training may have added value to improve the gait pattern, but future research is needed to examine whether the current findings can be replicated using commercially available robotic gait trainers or other rehabilitation technologies. Still, it is important to note that the use of technology in gait rehabilitation cannot replace the role of the physical therapist. Regardless of the technology used, it is the therapist who is responsible for guiding the training process, choosing adequate training settings, and motivating participants to reach their goals.

References

1. Harkema SJ, Behrman AL, Barbeau H. Locomotor Training: Principles and Practice, 1st ed. New York, NY: Oxford University Press; 2011.
2. Schmidt RA, Lee TD. Motor control and learning: A behavioral emphasis, 3rd ed. Champaign, IL, US: Human Kinetics; 1999.
3. Vashista V, Mustafa SK, Agrawal SK. Experimental studies on the human gait using a tethered pelvic assist device (T-PAD). IEEE Int Conf Rehabil Robot. 2011;2011:5975472.
4. Veneman JF, van Asseldonk EHF, Ekkelenkamp R, van der Helm FCT, van der Kooij Hi. Evaluation of the effect on walking of balance-related degrees of freedom in a robotic gait training device. IEEE Int Conf Rehabil Robot. 2007; 2007.
5. Meuleman J, van Asseldonk E, van Oort G, Rietman H, van der Kooij H. LOPES II--Design and Evaluation of an Admittance Controlled Gait Training Robot With Shadow-Leg Approach. IEEE Trans Neural Syst Rehabil Eng. 2016;24(3):352-363.
6. Zanotto D, Stegall P, Agrawal SK. ALEX III: A novel robotic platform with 12 DOFs for human gait training. IEEE Int Conf Robot Automat. 2013; 2013.
7. Aprile I, Iacovelli C, Goffredo M, et al. Efficacy of end-effector Robot-Assisted Gait Training in subacute stroke patients: Clinical and gait outcomes from a pilot bi-centre study. NeuroRehabilitation. 2019;45(2):201-212.
8. Stolz R, Nayyar R, Louie J, Bower KJ, Paul SK, Ng L. The effectiveness of a novel cable-driven gait trainer (Robowalk) combined with conventional physiotherapy compared to conventional physiotherapy alone following stroke: a randomised controlled trial. Int J Rehabil Res. 2019;42(4):377-384.
9. Taveggia G, Borboni A, Mulé C, Villafañe JH, Negrini S. Conflicting results of robot-assisted versus usual gait training during postacute rehabilitation of stroke patients: a randomized clinical trial. Int J Rehabil Res. 2016;39(1):29-35.
10. Hidler J, Nichols D, Pelliccio M, et al. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair. 2009;23(1):5-13.
11. Aprile I, Iacovelli C, Padua L, et al. Efficacy of Robotic-Assisted Gait Training in chronic stroke patients: Preliminary results of an Italian bi-centre study. NeuroRehabilitation. 2017;41(4):775-782.
12. Bang DH, Shin WS. Effects of robot-assisted gait training on spatiotemporal gait parameters and balance in patients with chronic stroke: A randomized controlled pilot trial. NeuroRehabilitation. 2016;38(4):343-349.
13. Gandolfi M, Valè N, Dimitrova E, et al. Robot-Assisted Stair Climbing Training on Postural Control and Sensory Integration Processes in Chronic Post-stroke Patients: A Randomized Controlled Clinical Trial. Front Neurosci. 2019;13:1143.
14. Tanaka N, Matsushita S, Sonoda Y, et al. Effect of Stride Management Assist Gait Training for Poststroke Hemiplegia: A Single Center, Open-Label, Randomized Controlled Trial. J Stroke Cerebrovasc Dis. 2019;28(2):477-486.
15. Tanaka N, Saitou H, Takao T, et al. Effects of gait rehabilitation with a footpad-type locomotion interface in patients with chronic post-stroke hemiparesis: a pilot study. Clin Rehabil. 2012;26(8):686-695.
16. Uçar DE, Paker N, Buğdaycı D. Lokomat: a therapeutic chance for patients with chronic hemiplegia. NeuroRehabilitation. 2014;34(3):447-453.
17. Yeung LF, Ockenfeld C, Pang MK, et al. Randomized controlled trial of robot-assisted gait training with dorsiflexion assistance on chronic stroke patients wearing ankle-foot-orthosis. J Neuroeng Rehabil. 2018;15(1):51.
18. Hornby TG, Campbell DD, Kahn JH, Demott T, Moore JL, Roth HR. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. Stroke. 2008;39(6):1786-1792.

19. Kelley CP, Childress J, Boake C, Noser EA. Over-ground and robotic-assisted locomotor training in adults with chronic stroke: a blinded randomized clinical trial. Disabil Rehabil Assist Technol. 2013;8(2):161-168.
20. Park J, Chung Y. The effects of robot-assisted gait training using virtual reality and auditory stimulation on balance and gait abilities in persons with stroke. NeuroRehabilitation. 2018;43(2):227-235.
21. Stein J, Bishop L, Stein DJ, Wong CK. Gait training with a robotic leg brace after stroke: a randomized controlled pilot study. Am J Phys Med Rehabil. 2014;93(11):987-994.
22. Westlake KP, Patten C. Pilot study of Lokomat versus manual-assisted treadmill training for locomotor recovery post-stroke. J Neuroeng Rehabil. 2009;6:18.
23. Guzik A, Drużbicki M, Wolan-Nieroda A. Assessment of two gait training models: conventional physical therapy and treadmill exercise, in terms of their effectiveness after stroke. Hippokratia. 2018;22(2):51-59.
24. Mehta S, Pereira S, Viana R, et al. Resistance training for gait speed and total distance walked during the chronic stage of stroke: a meta-analysis. Top Stroke Rehabil. 2012;19(6):471-478.
25. Rodrigues-Baroni JM, Nascimento LR, Ada L, Teixeira-Salmela LF. Walking training associated with virtual reality-based training increases walking speed of individuals with chronic stroke: systematic review with meta-analysis. Braz J Phys Ther. 2014;18(6):502-512.
26. Massaad F, Lejeune TM, Detrembleur C. Reducing the energy cost of hemiparetic gait using center of mass feedback: a pilot study. Neurorehabil Neural Repair. 2010;24(4):338-347.
27. Caty GD, Detrembleur C, Bleyenheuft C, Deltombe T, Lejeune TM. Effect of simultaneous botulinum toxin injections into several muscles on impairment, activity, participation, and quality of life among stroke patients presenting with a stiff knee gait. Stroke. 2008;39(10):2803-2808.
28. Bonnyaud C, Pradon D, Boudarham J, Robertson J, Vuillerme N, Roche N. Effects of gait training using a robotic constraint (Lokomat®) on gait kinematics and kinetics in chronic stroke patients. J Rehabil Med. 2014;46(2):132-138.
29. Bonnyaud C, Zory R, Boudarham J, Pradon D, Bensmail D, Roche N. Effect of a robotic restraint gait training versus robotic conventional gait training on gait parameters in stroke patients. Exp Brain Res. 2014;232(1):31-42.
30. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. Lancet. 2011;377(9778):1693-1702.
31. Bernhardt J, Hayward KS, Kwakkel G, et al. Agreed Definitions and a Shared Vision for New Standards in Stroke Recovery Research: The Stroke Recovery and Rehabilitation Roundtable Taskforce. Neurorehabil Neural Repair. 2017;31(9):793-799.
32. Bonita R, Beaglehole R. Recovery of motor function after stroke. Stroke. 1988;19(12):1497-1500.
33. Good DC, Bettermann K, Reichwein RK. Stroke rehabilitation. Continuum (Minneap Minn). 2011;17(3):545-567.
34. Brodal A. Self-observations and neuro-anatomical considerations after a stroke. Brain. 1973;96(4):675-694.
35. Phan TG, Wright PM, Markus R, Howells DW, Davis SM, Donnan GA. Salvaging the ischaemic penumbra: more than just reperfusion? Clin Exp Pharmacol Physiol. 2002;29(1-2):1-10.
36. Feeney DM, Baron JC. Diaschisis. Stroke. 1986;17(5):817-830.
37. Pennycott A, Wyss D, Vallery H, Klamroth-Marganska V, Riener R. Towards more effective robotic gait training for stroke rehabilitation: a review. J Neuroeng Rehabil. 2012;9:65.
38. Buurke JH, Nene AV, Kwakkel G, Erren-Wolters V, Ijzerman MJ, Hermens HJ. Recovery of gait after stroke: what changes? Neurorehabil Neural Repair. 2008;22(6):676-683.
39. Den Otter AR, Geurts AC, Mulder T, Duysens J. Gait recovery is not associated with changes in the temporal patterning of muscle activity during treadmill walking in patients with post-stroke hemiparesis. Clin Neurophysiol. 2006;117(1):4-15.
40. Kwakkel G, Kollen B, Lindeman E. Understanding the pattern of functional recovery after stroke: facts and theories. Restor Neurol Neurosci. 2004;22(3-5):281-299.
41. Taub E. Movement in nonhuman primates deprived of somatosensory feedback. Exerc Sport Sci Rev. 1976;4:335-374.
42. Taub E, Uswatte G, Mark VW, Morris DM. The learned nonuse phenomenon: implications for rehabilitation. Eura Medicophys. 2006;42(3):241-256.
43. Awad LN, Reisman DS, Kesar TM, Binder-Macleod SA. Targeting Paretic Propulsion to Improve Poststroke Walking Function: A Preliminary Study. Arch Phys Med Rehabil. 2014;95(5):840-848.
44. Hsiao HY, Awad LN, Palmer JA, Higginson JS, Binder-Macleod SA. Contribution of Paretic and Nonparetic Limb Peak Propulsive Forces to Changes in Walking Speed in Individuals Poststroke. Neurorehabil Neural Repair. 2016;30(8):743-752.
45. Veneman JF, Kruidhof R, Hekman EE, Ekkelenkamp R, Van Asseldonk EH, van der Kooij H. Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng. 2007;15(3):379-386.
46. Beets IA, Macé M, Meesen RL, Cuypers K, Levin O, Swinnen SP. Active versus passive training of a complex bimanual task: is prescriptive proprioceptive information sufficient for inducing motor learning? PLoS One. 2012;7(5):e37687.
47. Aurich-Schuler T, Grob F, van Hedel HJA, Labruyère R. Can Lokomat therapy with children and adolescents be improved? An adaptive clinical pilot trial comparing Guidance force, Path control, and FreeD. J Neuroeng Rehabil. 2017;14(1):76.
48. Lefeber N, De Buyzer S, Dassen N, De Keersmaecker E, Kerckhofs E, Swinnen E. Energy consumption and cost during walking with different modalities of assistance after stroke: a systematic review and meta-analysis. Disabil Rehabil. 2020;42(12):1650-1666.
49. Lefeber N, Swinnen E, Kerckhofs E. The immediate effects of robot-assistance on energy consumption and cardiorespiratory load during walking compared to walking without robot-assistance: a systematic review. Disabil Rehabil Assist Technol. 2017;12(7):657-671.
50. Fricke SS, Bayón C, der Kooij HV, EH FvA. Automatic versus manual tuning of robot-assisted gait training in people with neurological disorders. J Neuroeng Rehabil. 2020;17(1):9.
51. Skilbeck CE, Wade DT, Hewer RL, Wood VA. Recovery after stroke. J Neurol Neurosurg Psychiatry. 1983;46(1):5-8.
52. Wade DT, Hewer RL. Functional abilities after stroke: measurement, natural history and prognosis. J Neurol Neurosurg Psychiatry. 1987;50(2):177-182.
53. Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1995;76(1):27-32.
54. Bruni MF, Melegari C, De Cola MC, Bramanti A, Bramanti P, Calabrò RS. What does best evidence tell us about robotic gait rehabilitation in stroke patients: A systematic review and meta-analysis. J Clin Neurosci. 2018;48:11-17.
55. Cho JE, Yoo JS, Kim KE, et al. Systematic Review of Appropriate Robotic Intervention for Gait Function in Subacute Stroke Patients. Biomed Res Int. 2018;2018:4085298.
56. Mehrholz J, Thomas S, Kugler J, Pohl M, Elsner B. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev. 2020;10:CD006185.
57. Moucheboeuf G, Griffier R, Gasq D, et al. Effects of robotic gait training after stroke: A meta-analysis. Ann Phys Rehabil Med. 2020;63(6):518-534.
58. Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. Phys Ther. 1984;64(1):35-40.
59. Pavei G, Seminati E, Cazzola D, Minetti AE. On the Estimation Accuracy of the 3D Body Center of Mass Trajectory during Human Locomotion: Inverse vs. Forward Dynamics. Front Physiol. 2017;8:129.
60. Donelan JM, Kram R, Kuo AD. Simultaneous positive and negative external mechanical work in human walking. J Biomech. 2002;35(1):117-124.

6

Nederlandse samenvatting

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Veel mensen ervaren problemen met lopen na een cerebrovasculair accident (CVA, ook wel beroerte genoemd). Voorbeelden van zulke problemen zijn een lagere loopsnelheid, een ongelijke staplengte en afwijkend looppatroon. Om de loopvaardigheid van mensen na een CVA te verbeteren wordt normaal gesproken zo vroeg mogelijk in het revalidatietraject gestart met fysiotherapie. Het effect van reguliere fysiotherapie op het verbeteren van het looppatroon (als product van de kinematica (gewrichtshoeken) en kinetica (geleverde krachten en momenten) tijdens het lopen) is echter beperkt bij mensen na een CVA. Naast reguliere fysiotherapie wordt daarom tegenwoordig steeds vaker robotische looptraining aangeboden tijdens de revalidatie van mensen na een CVA. Een voorbeeld van een hiervoor gebruikte looprobot is de LOPES II. LOPES II bestaat uit een exoskelet, gecombineerd met een loopband en een systeem voor gewichtsondersteuning. De LOPES II biedt nieuwe mogelijkheden voor het trainen en verbeteren van het looppatroon van mensen in de subacute en chronische fase na een CVA, omdat deze looprobot meer vrijheidsgraden toestaat en alleen waar nodig de specifieke (aangedane) aspecten van het looppatroon ondersteunt (volgens het '*assist-as-needed*' principe). Deze ondersteuning kan daarbij zowel in het frontale als sagittale vlak worden geboden.

Het doel van dit proefschrift is tweeledig. Allereerst is het effect van het toelaten van extra vrijheidsgraden in een looprobot bij gezonde volwassenen onderzocht (hoofdstuk 2). Daarnaast is gekeken of intensieve training in de LOPES II het looppatroon kan verbeteren bij mensen in diverse fasen na CVA (hoofdstuk 3-5).

Bekkenbewegingen spelen een belangrijke rol bij de gewichtsverplaatsing en de balans tijdens het lopen en zijn daarom een belangrijk aandachtspunt tijdens de revalidatie van mensen na een CVA. Verrassend genoeg staan niet alle looprobots dergelijke bekkenbewegingen toe. In **hoofdstuk 2** wordt het effect van een 20-minuten durende training in de LOPES II op het looppatroon van gezonde volwassenen beschreven, waarbij de zijwaartse bekkenbewegingen en de bekkenrotaties tijdens de training ofwel volledig werden beperkt ofwel werden toegestaan en ondersteund door de looprobot. Het beperken van de bekkenbewegingen tijdens de training resulteerde na afloop in een kortdurende verandering van het looppatroon op vlak terrein. Na de training liepen de gezonde volwassenen met minder zijwaartse bekkenbewegingen en een smallere stapbreedte dan na afloop van de training waarin de bekkenbewegingen werden ondersteund. Deze afname in zijwaartse bekkenbeweging en stapbreedte was alleen zichtbaar tijdens de eerste vijf stappen na de training. Na tien stappen waren de bekkenbewegingen en de stapbreedte genormaliseerd en niet langer verschillend van het looppatroon zoals gemeten voorafgaand aan de training. Het beperken dan wel ondersteunen van de bekkenbewegingen tijdens de looptraining had geen effect op de kinematica van het lopen of op de overige spatiotemporele loopparameters. We concludeerden dat training in een looprobot die de bekkenbewegingen beperkt leidt tot een direct, doch kortdurend negatief effect op het looppatroon van gezonde volwassenen, terwijl het toestaan en ondersteunen van de bekkenbewegingen tijdens de looptraining resulteert in een meer natuurlijk looppatroon nadien.

In **hoofdstuk 3** worden de resultaten van een geblindeerde en gerandomiseerde studie beschreven waarin de effecten van een zes weken durende looptraining gericht op het verbeteren van specifieke aspecten van het looppatroon in de LOPES II (experimentele groep, N=17) werden vergeleken met reguliere fysiotherapie (controle groep, N=15) bij mensen in de subacute fase (< 10 weken) na CVA die in staat waren om enkele passen te lopen zonder fysieke hulp. Voorafgaand aan de start van de looptraining werd voor elke deelnemer een individueel trainingsdoel bepaald. Deze trainingsdoelen waren gericht op het verbeteren van 1) het loskomen van de voet van de grond in de zwaaifase (*foot clearance*), 2) de stabiliteit in de standfase, 3) gewichtname tijdens de standfase, of 4) het voorbereiden van de voetlanding aan het einde van de zwaaifase. In beide groepen nam de geleverde externe mechanische arbeid (maat voor mechanische efficiëntie van het lopen) af na afloop van de looptraining (T1) ten opzichte van de voormeting (T0). Deze afname was vier maanden na afloop van de looptraining (T2) niet meer zichtbaar. De loopsnelheid was in beide groepen toegenomen op T1 en T2 vergeleken met T0. Verder lieten beide groepen een verbetering zien op de meeste spatiotemporele loopparameters, functionele looptaken en klinische uitkomsten op T1 en T2 ten opzichte van T0. Afgezien van een toename in de stapbreedte na afloop van de reguliere fysiotherapie (T1) en een grotere staplengte van het aangedane (paretische) been na afloop van de LOPES II training (T2) waren er geen significante verschillen tussen de groepen zichtbaar. Een subanalyse van deelnemers met een trainingsdoel gericht op het verbeteren van het loskomen van de voet in de zwaaifase (N=12), liet een grotere toename in de knieflexiehoek tijdens de zwaaifase zien bij deelnemers na afloop van de looptraining in LOPES II in vergelijking met deelnemers aan de reguliere fysiotherapiebehandeling. Er werden geen kinematische verschillen gevonden tussen de trainingsgroepen bij deelnemers met een trainingsdoel gericht op het verbeteren van de stabiliteit in de standfase (N=13). Vanwege de kleine groepsgrootte was het niet mogelijk om een subanalyse uit te voeren op de data van de deelnemers met een individueel trainingsdoel gericht op de gewichtname tijdens de standfase (N=6) of gericht op het voorbereiden van voetlanding aan het einde van de zwaaifase (N=1). We concludeerden dat het effect van robotische looptraining voor het verbeteren van het looppatroon van mensen in de subacute fase na een CVA in het algemeen niet superieur is aan dat van reguliere fysiotherapie, maar dat robotische looptraining mogelijk wel effectiever is dan reguliere fysiotherapie voor het verbeteren van specifieke aspecten van het looppatroon, zoals de knieflexiehoek tijdens de zwaaifase.

Hoofdstuk 4 beschrijft de resultaten van een systematisch literatuuronderzoek naar de effectiviteit van interventies gericht op het verbeteren van de afzetkracht (propulsie) en/of enkelkinetica van het paretische been in relatie tot de loopsnelheid van mensen in de subacute of chronische fase na een CVA. Deze studies onderzochten het effect van bewegingsinterventies (N=25), operaties (N=2), of het gebruik van niet-invasieve hersenstimulatie (N=1). In acht studies was de interventie primair gericht op het verbeteren van de paretische propulsie. Zes studies waren van een hoge kwaliteit (op basis van de Downs&Black schaal). Het effect van de interventies varieerde sterk tussen de studies, waarbij de helft van de studies (N=14) een verbetering van de propulsie en/of enkelkinetica rapporteerde na afloop van de interventie. Het merendeel van de studies rapporteerde een verbetering van de loopsnelheid. De verbetering van de propulsie werd vooral gevonden na interventies die de inzet van latente propulsiecapaciteit van het paretische been ontlokten. Aangezien de loopsnelheid in veel studies toenam, ongeacht het effect van de interventie op de propulsie van het paretisch been, suggereren de resultaten van dit literatuuronderzoek dat de meeste mensen na een CVA hun loopsnelheid vergroten door gebruik te maken van compensatiemechanismen (b.v. het vergroten van de propulsie van het niet-paretische been) in plaats van het vergroten van de propulsie van het paretische been.

In **hoofdstuk 5** wordt het effect van een vijf weken durende looptraining in LOPES II (60 minuten, twee keer per week) geëvalueerd. De looptraining was gericht op het verbeteren van de propulsiesymmetrie middels het verbeteren van de propulsie van het paretische been bij mensen in de chronische fase (>6 maanden) na CVA. Naast de looptraining in LOPES II deden de deelnemers dagelijks thuis oefeningen (15 minuten per dag) gericht op het vergroten van de kuitkracht en het toepassen van de geleerde strategieën tijdens het lopen in het dagelijkse leven. Tijdens de vijf weken voorafgaand aan de looptraining waren er, afgezien van een toename in de loopsnelheid, geen veranderingen zichtbaar in de loopparameters. Na afloop van de looptraining was de propulsiesymmetrie verbeterd doordat de propulsie van het paretische been was toegenomen. Deelnemers met de grootste verbetering in propulsiesymmetrie waren degenen die voorafgaand aan de start van de looptraining met een grotere propulsieasymmetrie liepen. De hoek van het afzetbeen met de verticaal, en het plantairflexiemoment van de enkel waren ook verbeterd na afloop van de looptraining. Tot slot werd na afloop van de looptraining een toename gevonden van de loopsnelheid, de uitvoering van functionele looptaken, en het activiteitenniveau gemeten in het dagelijks leven. De positieve effecten van de looptraining waren vijf weken nadien nog aanwezig, waarbij de loopsnelheid zelfs nog verder was verbeterd. De resultaten van dit onderzoek laten zien dat robotische looptraining effectief kan zijn voor het aanwenden van latente propulsiecapaciteit van het paretische been bij mensen in de chronische fase na een CVA, waarbij niet alleen de propulsiesymmetrie en loopsnelheid verbeteren, maar ook de uitvoer van functionele looptaken en het activiteitenniveau in het dagelijkse leven.

Conclusies

De resultaten van dit proefschrift laten zien dat het mogelijk is om specifieke aspecten van het looppatroon van mensen na een CVA te verbeteren door het gebruik van compensatie mechanismen te voorkomen (in de subacute fase) of te verminderen (in de chronische fase), en het gebruik van de latente capaciteit van het paretische been te optimaliseren. Looprobots met voldoende vrijheidsgraden, zoals de LOPES II, bieden de mogelijkheid om een trainingsomgeving te creëren waarin aan de voorwaarden voor het lopen wordt voldaan, zodat de deelnemers zich volledig kunnen focussen op de specifieke, te trainen aspecten van het looppatroon. Aanvullend onderzoek is nodig om vroeg in de revalidatie te kunnen bepalen voor welke mensen na een CVA dergelijke training meerwaarde heeft boven reguliere fysiotherapie.

Dankwoord

Dankwoord

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Lieve Carien, Rolinde en Wilrieke. Wat is het heerlijk om drie van zulke leuke zussen te hebben! Jullie staan altijd voor mij klaar, en dat waardeer ik enorm. Bedankt voor jullie luisterende oor, relativeringsvermogen, en alle goede adviezen. Ik ben trots op jullie en jullie mooie gezinnen. Carien, als ervaringsdeskundige weet je als geen ander wat promoveren inhoudt. Wat is het daarom fijn dat je mij vandaag als paranimf wilt ondersteunen! Rolinde, wat is het altijd fijn om mijn hoofd leeg te maken tijdens de vele in/ontspannende ritjes op de racefiets. Wilrieke, dat jij mijn paranimf zou gaan worden stond bij mijn aanstelling natuurlijk al vast. Ik kijk met heel veel goede herinneringen terug op al onze logeerweekendjes en vakanties, de vele gezellige wandeluurtjes voorafgaand aan en tijdens de vierdaagse, de ellenlange telefoongesprekken, en alle andere avonturen die we in de loop der jaren hebben meegemaakt. Laten we er nog vele aan toe gaan voegen, nu ik weer zeeën van tijd heb!!

Curriculum vitae

Curriculum vitae

Jolanda Alingh was born in Groningen on September 9th, 1992. After graduating from secondary school (Ubbo Emmius, Stadskanaal) in 2010, she started the bachelor Human Movement Sciences at the University of Groningen. During her master Human Movement Sciences, with a specialization on ‘Rehabilitation and functional recovery’, she became highly interested in the use of new technology in gait rehabilitation. Jolanda performed her research internship at the University of Twente and Roessingh Center for Rehabilitation (Enschede). Under supervision of dr. Edwin van Asseldonk and dr. Rob den Otter, she investigated the immediate effect of pelvic support in the robotic gait trainer LOPES II on gait symmetry and muscle activation patterns in subacute stroke survivors. In 2016, Jolanda received her master’s degree. In 2015, she started as a PhD candidate on the *LOPES-Arts* project at the Sint Maartenskliniek and Radboudumc in Nijmegen. In 2016, she received additional funding, together with Prof. Sander Geurts, dr. Vivian Weerdesteyn and dr. Brenda Groen, for a study on the effect of robotic gait training for improving paretic leg propulsion in individuals in the chronic phase after stroke. Currently, she is working as a data analyst at Merem Medische Revalidatie in Hilversum.

List of publications

List of publications

Publications

Alingh JF, Weerdesteyn V, Nienhuis B, Van Asseldonk EHF, Geurts ACH, Groen BE. Immediate after-effects of robot-assisted gait with pelvic support or pelvic constraint on overground walking in healthy subjects. J Neuroeng Rehabil. 2019 Mar 15;16(1):40.

Alingh JF*, Fleerkotte BM*, Groen BE, Rietman JS, Weerdesteyn V, Van Asseldonk EHF, Geurts ACH*, Buurke JH*. Effect of assist-as-needed robotic gait training on the gait pattern post stroke: a randomized controlled trial. J Neuroeng Rehabil. 2021 Feb 5;18(1):26.
**These authors contributed equally to this work*

Alingh JF, Groen BE, Van Asseldonk EHF, Geurts ACH, Weerdesteyn V. Effectiveness of rehabilitation interventions to improve paretic propulsion in individuals with stroke - A systematic review. Clin Biomech (Bristol, Avon). 2020 Jan;71:176-188.

Alingh JF, Groen BE, Kamphuis JF, Geurts ACH, Weerdesteyn V. Task-specific training for improving propulsion symmetry and gait speed in people in the chronic phase after stroke: a proof-of-concept study. J Neuroeng Rehabil. 2021 Apr 23;18(1):69.

Conference abstracts

JF Alingh, AR den Otter, BE Groen, EHF van Asseldonk. The effect of mediolateral pelvic support on gait symmetry and muscle activation patterns of subacute stroke patients walking in LOPES II. NeuroCIMT IMDI NeuroControl Symposium, Egmond aan Zee, 2016 (poster presentation).

V Weerdesteyn, **JF Alingh**, B Nienhuis, BE Groen, ACH Geurts. Support vs. pelvic constraints: Immediate after effects of robot assisted gait training in LOPES II on overground walking in healthy subjects. ISPGR World Congress, Fort Lauderdale, Florida, 2017 (poster presentation).

JF Alingh, BE Groen, B Nienhuis, V Weerdesteyn, ACH Geurts. Immediate after effects of pelvic support and pelvic constraints during robot assisted gait training in LOPES II on overground walking in healthy subjects. NeuroRehabilitation and Neural Repair, Maastricht, 2017 (poster presentation).

JF Alingh, BE Groen, EHF van Asseldonk, V Weerdesteyn, ACH Geurts. Rehabilitation interventions to improve paretic propulsion in individuals after stroke – a systematic review. RehabMove Congress, Groningen, 2018 (poster presentation); Donders Institute for Brain Cognition and Behaviour - Poster Session, Nijmegen, 2018 (poster presentation).

JF Alingh, BE Groen, B Nienhuis, V Weerdesteyn, ACH Geurts. Internal, external and total mechanical work during walking at comfortable and lower velocities in healthy adults: preliminary results. Donders Institute for Brain Cognition and Behaviour – Donders Discussions, Nijmegen, 2018 (poster presentation); Roessingh Research and Development Symposium – Enabling Technology for Active Life and Better Health, Enschede, 2018 (poster presentation) – Best Poster Award.

JF Alingh, BE Groen, V Weerdesteyn, ACH Geurts. Effectiveness of a robot-assisted gait training in subacute stroke survivors. Donders Institute for Brain Cognition and Behaviour – Donders Discussions, Nijmegen, 2019 (oral presentation).

PhD portfolio

PhD Portfolio

Name PhD student: Jolanda F. Alingh
Department: Research (Sint Maartenskliniek)
Graduate school: Donders Graduate School

TRAINING ACTIVITIES	Year(s)	ECTS
a) **Courses and Workshops**		
- Vicon hardware & software	2016	0.33
- Basiscursus regelgeving en organisatie klinisch onderzoek (BROK)	2016	1.5
- NeuroControl summer school	2016, 2017	3.4
- Masterclass patiëntparticipatie	2017	0.33
- Scientific integrity course	2017	0.33
- Donders graduate school introduction day	2017	0.33
- Management voor Promovendi	2017	2.0
- Cambridge Advanced English	2017	3.0
- Scientific Writing for PhD Candidates	2018	3.0
- Graduate school day	2018, 2019	0.66
- Presentation Skills	2018	1.5
- Loopbaanmanagement voor promovendi	2019	1.0
- EpidM K73 Longitudinale data-analyse	2019	1.0
- The Art of Finishing Up	2019	1.0
- Design and Illustration	2019	1.0
- BROK herregistratie	2021	0.15
b) **Seminars and Lectures**	2015-2020	1.1
c) **(Inter)national Symposia and Congresses**		
- NeuroCIMT and IMDI NeuroControl symposium	2016	0.75
- Roessingh Research and Development symposium	2016, 2018	0.75
- 2nd Congress on NeuroRehabilitation and Neural Repair	2017	1.25
- Donders Discussions	2018, 2019	1.5
- Society for Movement Analysis Laboratories in the Low Lands (SMALLL) congress	2018	0.25
- 6th RehabMove Congress		
- Donders Institute poster session	2018	1.25
d) **Other**		
- Research lunch Sint Maartenskliniek	2016-2019	2.0
- Journal club Sint Maartenskliniek and Radboudumc	2018-2020	2.0
TEACHING ACTIVITIES	Year(s)	ECTS
e) **Supervision of internships**		
- Supervision of master student Biomedical Sciences	2017-2018	3.0
- Supervision of bachelor student Biomedical Sciences	2019	2.0
f) **Other**		
- Presentation and demo LOPES	2016-2019	1.0
TOTAL		**38.15**

Research data management

Research data management

General information about the data collection

This research followed the applicable laws and ethical guidelines. Research data management was conducted according to the FAIR principles. The paragraphs below specify in detail how this was achieved.

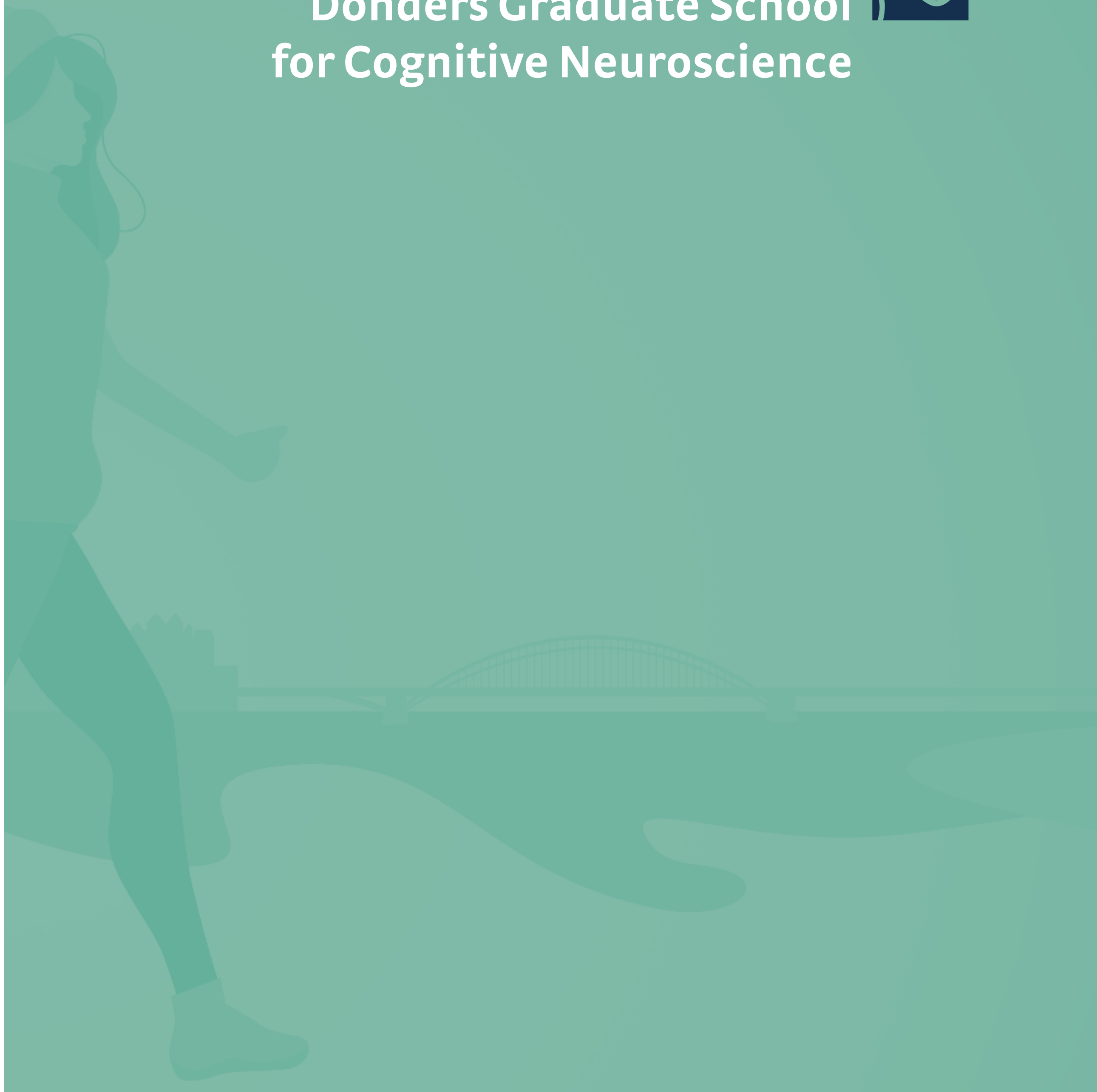
Ethics and privacy

Chapters 2, 3 and 5 were based on the results of human studies that were conducted in accordance with the principles of the Declaration of Helsinki. The corresponding study protocols were approved by the Medical and Ethical Review board Committee (MREC) on Research Involving Human Subjects Twente, Enschede, the Netherlands (Chapters 2 and 3) or Region Arnhem Nijmegen, Nijmegen, the Netherlands (Chapter 5). Additionally, manufacturer MOOG notified the Health Care and Youth Inspectorate (IGJ) of the clinical investigations involving the medical device LOPES II. The studies described in Chapters 3 and 5 were registered in the Dutch Trial Register (NTR5060) and ClinicalTrials.gov (NCT04650802), respectively. Our systematic review (Chapter 4) fell outside the scope of the medical research involving human subjects act. Written informed consent was obtained from all study participants prior to any study procedure. The privacy of the participants in all studies of this thesis was warranted using encrypted and unique individual subject codes. The encrypted keys were stored separately from the research data and were only accessible to members of the project who needed access based on their role within the project.

FAIR principles

Findable: Data were stored on the server of the research department at the Sint Maartenskliniek: 'V:\research_reva_studies\637_LOPES-ARTS' and 'V:\research_reva_studies\785_LOPES_IPICS'. The paper CRF files were stored at the research department of the Sint Maartenskliniek (room W0.09) and were/are transferred to the department's archive after study publication.
Accessible: All data are available on reasonable request by contacting the staff secretary at the research department of the Sint Maartenskliniek (secretariaat.research@maartenskliniek.nl) or the corresponding author.
Interoperable: Documentation was added to the data sets to make the data interpretable. The documentation contains links to publications, references to the location of the data sets and description of the data sets. The data was stored in the following formats: .xlsx (Microsoft Office Excel) and .mat (MATLAB, Mathworks, USA). No existing data standards were used such as vocabularies, ontologies or thesauri.
Reusable: The data will be stored for at least 15 years. Use of these data in future research is only possible after a renewed permission by the patients as recorded in their informed consents.

Donders Graduate School for Cognitive Neuroscience



Donders Graduate School for Cognitive Neuroscience

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioral science, medicine and related disciplines. Selective admission and assessment centers guarantee the enrolment of the best and most motivated students.

DGCN tracks the career of PhD graduates carefully. More than 50% of PhD alumni show a continuation in academia with postdoc positions at top institutes worldwide, e.g. Stanford University, University of Oxford, University of Cambridge, UCL London, MPI Leipzig, Hanyang University in South Korea, NTNU Norway, University of Illinois, North Western University, Northeastern University in Boston, ETH Zürich, University of Vienna etc.. Positions outside academia spread among the following sectors: specialists in a medical environment, mainly in genetics, geriatrics, psychiatry and neurology. Specialists in a psychological environment, e.g. as specialist in neuropsychology, psychological diagnostics or therapy. Positions in higher education as coordinators or lecturers. A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high-quality positions that play an important role in our knowledge economy.

More information on the DGCN as well as past and upcoming defenses please visit:
http://www.ru.nl/donders/graduate-school/phd/

Theses Sint Maartenskliniek

Theses Sint Maartenskliniek

Van Dijsseldonk, R. (2021). *Step into the future: mobility after spinal cord injury*. Radboud University Nijmegen, Nijmegen, The Netherlands.

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Bouman, C. (2018). *Dose optimisation of biologic DMARDs in rheumatoid arthritis: long-term effects and possible predictors.* Radboud University Nijmegen, The Netherlands.

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Hendricks, H. (2003). *Motor evoked potentials in predicting motor and functional outcome after stroke.* University of Nijmegen, Nijmegen, The Netherlands.

Hosman, A. J. F. (2003). *Idiopathic thoracic spinal deformities and compensatory mechanisms.* University of Nijmegen, Nijmegen, The Netherlands.

Donker, S. (2002). F*lexibility of human walking: a study on interlimb coordination.* Groningen University, Groningen, The Netherlands.

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Geurts, A. (1992). *Central adaptation of postural organization to peripheral sensorimotor impairments.* University of Nijmegen, Nijmegen, The Netherlands.

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